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Contents

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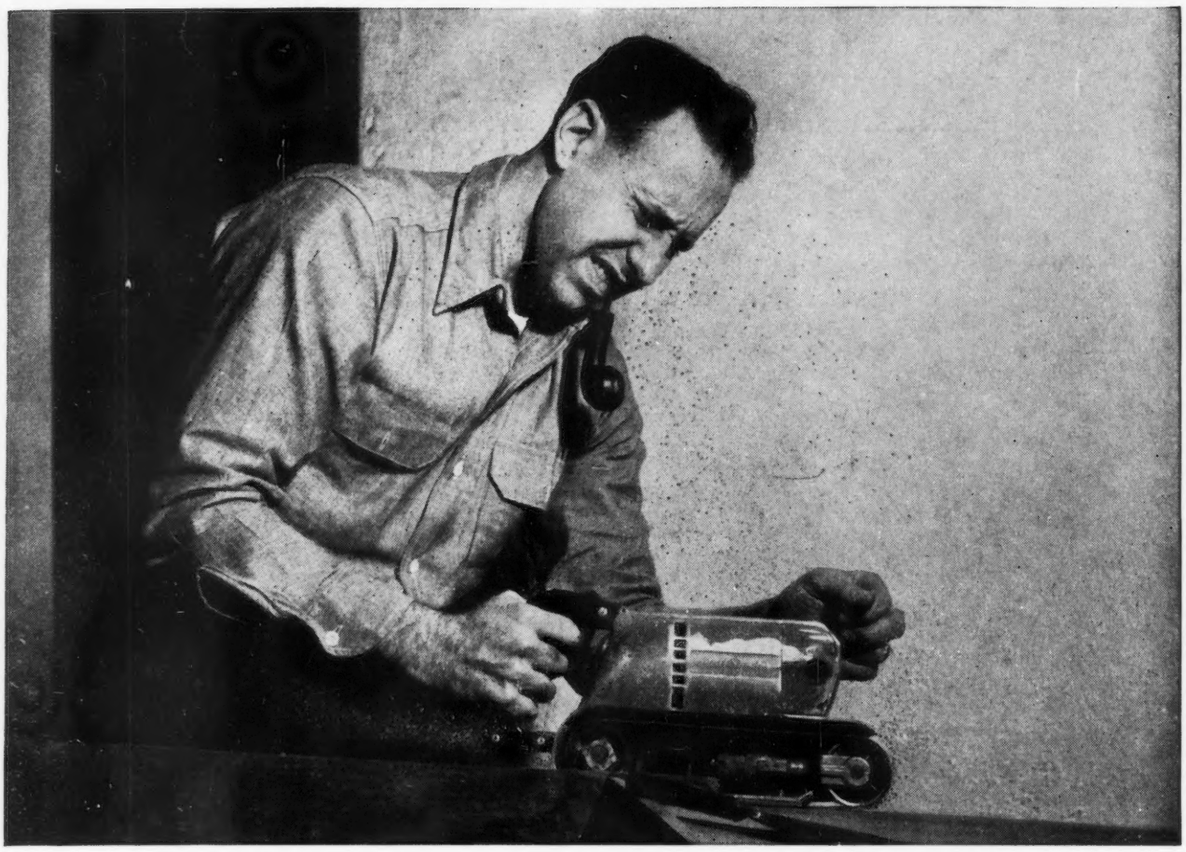

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Thirty Years Ago . . .

From the Journal of June, 1926

(Extract from a letter from a Canadian doctor travelling in Italy):

"It was very unfortunate that Mussolini was injured after delivering his address of welcome to our Association (International Surgical). I shook hands with him five minutes before he was wounded. His address impressed me most favourably. He has a fine manly dignified presence, a pleasing voice and his matter was excellent. He is doing wonders for Italy and indeed for the world in saving Italy from Bolshevism. He has all the better Italians behind him and is carrying into effect the best Italian ideals."

Federation of Medical Women. Organization of the medical women of Canada as a national federation having affiliation with the Medical Women's International Association has been under consideration for some years past, and an informal preliminary meeting was held in Montreal in June 1923. As a result of action then taken and of an urgent request from the British Federation of Medical Women for Canadian representation at the meeting of the Medical Women's International Association in London in 1924, an organizing meeting was held in Ottawa in June 1924 during the meeting of the C.M.A.

British Columbia. Dr. J. H. MacDermot of Vancouver has been appointed to represent the B.C. Medical Association on the Board of Trustees in connection with the proposed Preventorium, to which the Rotary Club of Vancouver has given $10,000.

point of departure

for the selective treatment of

hypertension

"ALSERIN"

BRAND OF

CRYSTALLINE RESERPINE

an economical preparation which

- **lowers blood pressure**
- **slows the heart rate**
- **tranquilizes**

FOR THE TREATMENT OF SEVERE HYPERTENSION SEE INSIDE » » »

SIDE EFFECTS

Alserin is tolerated in large doses by experimental animals, marked sedation being the most prominent effect. Clinically, in rare instances, full therapeutic doses may cause mental depression. Disturbing dreams and nightmares occur not infrequently. Stuffiness of the nose may occur and may disappear spontaneously with reduction of the dose. Gastric acid secretion is sometimes increased. If administered to patients with gastric ulcer, Alserin should be accompanied by simultaneous antacid and anti-secretory therapy.

"ALSERIN" 0.1 mg.
TABLET NO. 845 "Frosst"

"ALSERIN" 0.25 mg.
TABLET NO. 395 "Frosst"

DOSAGE: Initially, 0.25 to 0.5 mg. two or three times daily may be required and the maintenance dosage may be as little as 0.3 to 0.5 mg. in the total daily dose.

Stuffiness of the nose frequently accompanies the administration of Alserin. This innocuous but unpleasant effect may be prevented by the simultaneous use of an antihistamine.

"ALSERIN-A" 0.25 mg.
TABLET NO. 843 "Frosst"

Crystalline reserpine	0.25 mg.
Carbinoxamine maleate	2.0 mg.

DOSAGE: Initially, 1 to 2 tablets two or three times daily may be required and the maintenance dosage may be as little as 1 to 2 tablets in the total daily dose.

ALL FORMULAE AVAILABLE IN BOTTLES OF 100 TABLETS

For the treatment of hypertension associated with increased capillary fragility.

"ALSERIN" COMPOUND
TABLET NO. 455 "Frosst"

Crystalline reserpine	0.25 mg.
Rutin NF	20 mg.
Ascorbic acid	30 mg.

DOSAGE: One or two tablets 2 or 3 times daily.

FOR THE TREATMENT OF HYPERTENSION ASSOCIATED WITH CORONARY INSUFFICIENCY.

"ALSERIN" COMPOUND
with
THEOPHYLLINE
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Crystalline reserpine	0.25 mg.
Rutin NF	20 mg.
Ascorbic acid	30 mg.
Theophylline	100 mg.

DOSAGE: One or two tablets 2 or 3 times daily.

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practical combined therapy

for the individualized treatment of

severe hypertension

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BRAND OF

CRYSTALLINE RESERPINE

"PROTOVAB" TABLET

BRAND OF

PROTOVERATRINES A and B

effective with greatly reduced hazard of untoward effects

Alserin and protoveratrines are mutually potentiating. In combined therapy the effective dose of each is smaller and the therapeutic-to-toxic ratio markedly widened. The side effects usually accompanying full therapeutic doses of protoveratrines, when used as the sole hypotensive drug, namely . . . epigastric and sub-sternal burning, unpleasant taste, salivation, sweating, hiccup, nausea and vomiting . . . are avoided.

There are many variations in regimen which may be used in combined therapy. The table shows one procedure. The quantities of the individual drugs may be varied to suit each individual.

"ALSERIN" 0.1 mg.

TABLET NO. 845 "Frosst"

"ALSERIN" 0.25 mg.

TABLET NO. 395 "Frosst"

Stuffiness of the nose frequently accompanies the administration of Alserin. This innocuous unpleasant effect may be prevented by the simultaneous use of an antihistamine.

"ALSERIN-A" 0.25 mg.

TABLET NO. 843 "Frosst"

Crystalline reserpine	0.25 mg.
Carbinoxamine maleate	2.0 mg.

"PROTOVAB" 0.2 mg.

TABLET NO. 886 "Frosst"

"PROTOVAB" 0.5 mg.

TABLET NO. 887 "Frosst"

Bottles of 100 tablets.

A METHOD OF COMBINATION THERAPY

Basic medication: usually one tablet ALSERIN 0.25 mg. after meals and before retiring.

"PROTOVAB" DOSE	After Breakfast	After Lunch	After Dinner	Before Bedtime	Remarks
1st trial	0.5 mg.	0	0	0.5 mg.	Determine effects after 2 or 3 days. If sub-optimal, proceed to 2nd trial.
2nd trial	0.5 mg.	0	0.5 mg.	0.5 mg.	Determine effects after 2 or 3 days. If sub-optimal, proceed to 3rd trial.
3rd trial	0.5 mg.	0.5 mg.	0.5 mg.	0.5 mg.	Side effects may be frequent at this level of dosage.

To determine maintenance dose, reduce doses of PROTOVAB in the same order as they were added by substituting one or two 0.2 mg. tablets for the 0.5 mg. tablet

CAUTION

Hypertension associated with pheochromocytoma and coarctation of the aorta is not improved with ALSERIN or PROTOVAB, and their use should be avoided. Severe mental depression also contraindicates the use of ALSERIN (reserpine). Overdosage of veratrum alkaloids can result in serious bradycardia and an excessive drop in blood pressure, either of which may be counteracted by the prompt injection of atropine or ephedrine.

Charles E. Frosst & Co.

Frosst

as a tranquilizing agent

"ALSERIN"

BRAND OF

CRYSTALLINE RESERPINE

in general practice

ALSERIN is recommended

- to establish a more tranquil background for specific therapy;
- to alleviate "problem" situations of emotional origin.

ALSERIN reduces irritability, lessens agitation, facilitates sleep, improves appetite, induces gain in weight, promotes tranquility.

It must be noted that in some patients long continued use of full therapeutic doses may cause severe mental depression.

in psychiatry

ALSERIN is recommended in the management of psychoses.
ALSERIN has a definite place in psychiatry. It is indicated in conditions in which anxiety and agitation complicate institutional management. Patients under treatment become co-operative and more readily amenable to psychiatric procedures.

ALSERIN improves chronically disturbed psychotic patients. In a group of 200 such patients 87% "showed some degree of improvement, and 71% did better with reserpine therapy than with electroshock."

Many mildly disturbed patients often benefit from relatively small doses, namely 0.1 to 0.25 mg., administered before retiring.

In the management of drug withdrawal symptoms following acute deprivation, ALSERIN helps to erase "the fearful mental aspects of narcotic withdrawal sickness."

"ALSERIN" 0.1 mg.
TABLET NO. 845 "Frosst"

"ALSERIN" 0.25 mg.
TABLET NO. 395 "Frosst"

"ALSERIN" 1 mg.
TABLET NO. 829 "Frosst"

Dosage
must be individualized.

In general practice — 0.1 to 1 mg. daily.
In psychiatry — 1 to 6 mg. daily.
In patients requiring minimal doses, medication may be administered in a single dose before retiring.

Stuffiness of the nose frequently accompanies the administration of Alserin. This innocuous but unpleasant effect may be prevented by the simultaneous use of an antihistamine.

"ALSERIN-A" 0.25 mg.
TABLET NO. 843 "Frosst"

Crystalline reserpine..... 0.25 mg.
Carbinoxamine maleate..... 2.0 mg.

"ALSERIN-A" 1 mg.
TABLET NO. 844 "Frosst"

Crystalline reserpine..... 1.0 mg.
Carbinoxamine maleate..... 4.0 mg.

ALL FORMULAE AVAILABLE IN BOTTLES OF 100 TABLETS

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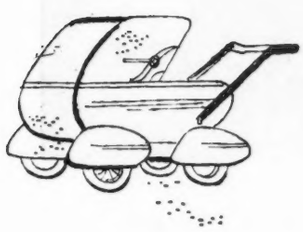
a favorite for over eighty years!



Baby's Own Soap is a pure soap, super fatted with a special extract of lanolin, to make it mild and gentle for the tender skin of babies. It contains no free caustic soda, no coloring agents or fillers. Thorough tests show that components of the perfume which gives Baby's Own its fresh and delicate aroma are entirely free of elements which would affect the normal skin of babies. Its rich lather gets baby's skin thoroughly clean and clears tiny pores of impurities.

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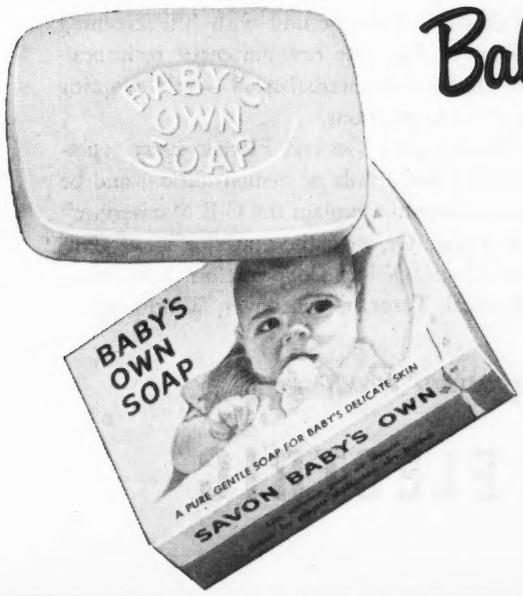
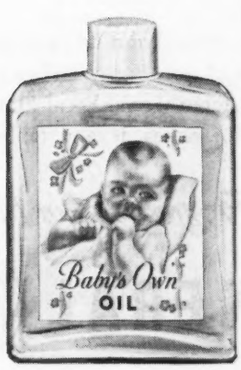
Baby's Own 3 step-care





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augmented by—Ascorbic acid: 20 mg.
plus—Aluminum hydroxide: 75 mg.

Clinical studies have shown that the concomitant administration of corticoids and salicylates not only enables a lower dose of each to be given to achieve an equal or better degree of therapeutic effect but also decreases the likelihood of undesirable effects. Sigmagen is of particular value in patients no longer responding to salicylates alone.

AVERAGE DOSAGE:
1 to 2 tablets 4 times daily after meals and at bedtime.

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OXYGEN THERAPY *News*

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Published monthly to make available to physicians information on reports in current medical literature on the use of oxygen. These digests reflect our understanding of the authors' findings. We suggest consulting the original reports, especially where clinical procedures are recommended.

Vol. XIII, No. 5

POSTOPERATIVE PULMONARY EDEMA: Chief factors concerned in the production of pulmonary edema are (1) increased pulmonary capillary permeability, usually due to anoxia; (2) increased hydrostatic pressure in the pulmonary capillaries; and (3) decreased osmotic pressure of the blood. Pulmonary edema can be recognized clinically by (1) onset, gradual or sudden; (2) oppression or pain in the chest; (3) apprehension; (4) dyspnea or orthopnea; (5) incessant short cough with copious frothy or blood-tinged sputum; (6) pallor; (7) perspiration; (8) rales throughout lungs; (9) blood pressure and pulse rate elevated in less severe case; and (10) blood pressure depressed in severe cases.

Pulmonary edema as a complication of surgery is found relatively infrequently at the present time, except in certain patients undergoing cardiac surgery. However, it is such a serious complication that every effort should be made to prevent its occurrence. Conditions predisposing towards pulmonary edema should be treated preoperatively. A high concentration of oxygen should be used during the operation with sufficient tidal volume to wash out the carbon dioxide. Oxygen should be administered postoperatively, the patient should be turned hourly, and deep breathing and early mobilization should be encouraged. Blood loss should be replaced on a cubic centimeter for cubic centimeter basis and intravenous fluids administered with caution. If pulmonary edema is feared, it is best to elevate the head of the patient as soon as possible.

If pulmonary edema occurs, prompt treatment is essential. Intermittent tourniquets to the extremities, phlebotomy, aminophyline, and morphine (unless specifically contraindicated) may all be useful. Anoxia must be strenuously treated. A snug-fitting face mask should be with an adequate flow of oxygen. Some recommend 40 to 50 per cent oxygen rather than 100 per cent mits exhalation against a sure may be helpful at should start at plus and the pressure one to four of the

ution, which Luisada considers to be the most beneficial anti-foaming agent (OXYGEN THERAPY NEWS, July 20, 1954). Salt restriction and other additional measures may be necessary to prevent recurrence of the edema. **Beattie, E.J.: Am. J. Surg. 89:310 (Feb) 1955.**

RALES AND ARTERIAL OXYGEN SATURATION: Arterial oxygen saturation was measured patients with heart disease, all of rales of varying extent indicating pulm gestion or edema. There was little between the arterial oxygen satura diffuseness of rales. In 7 patients w apparently widespread pulmonary terial oxygen saturation was greate cent. Several explanations are sugg

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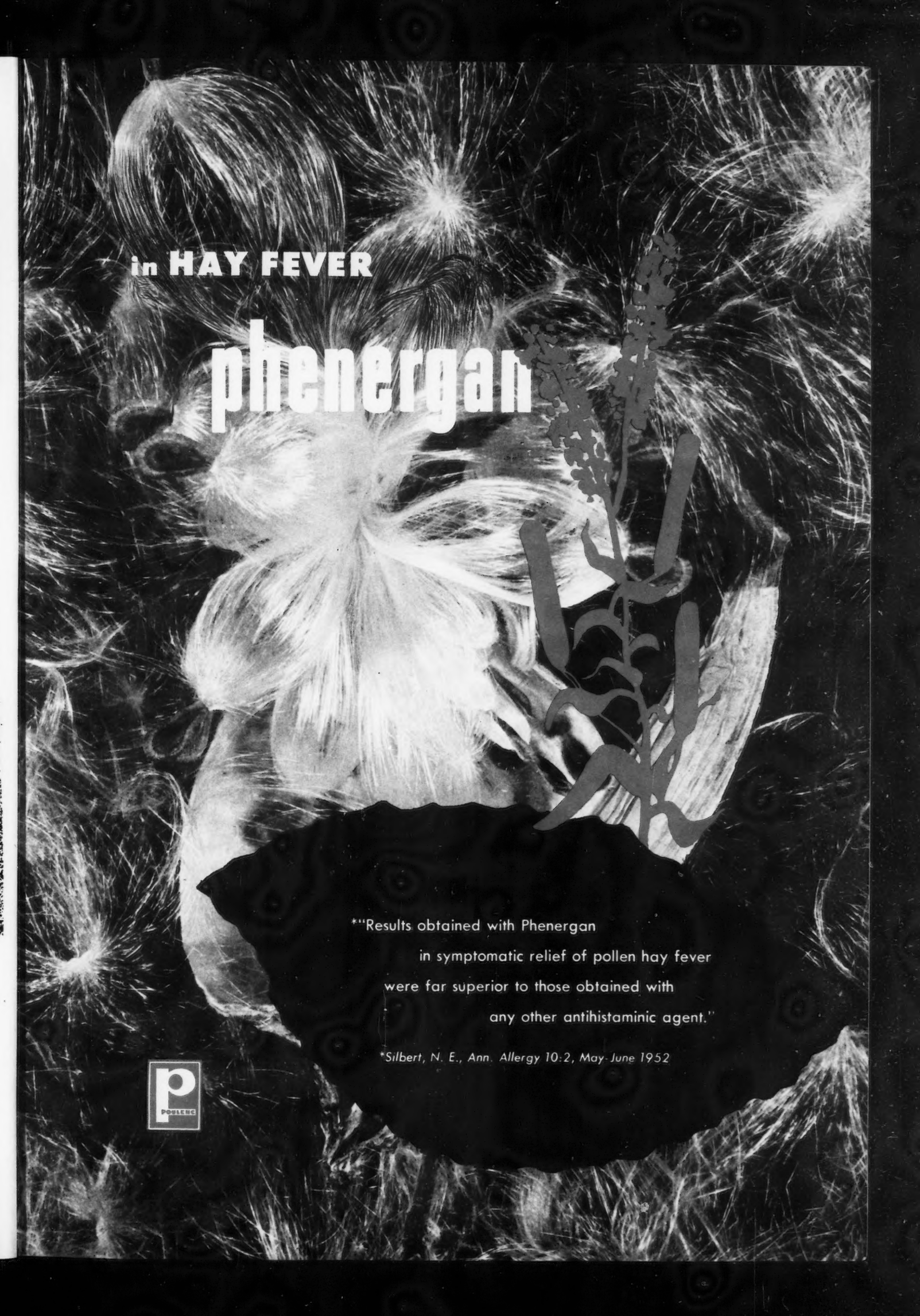
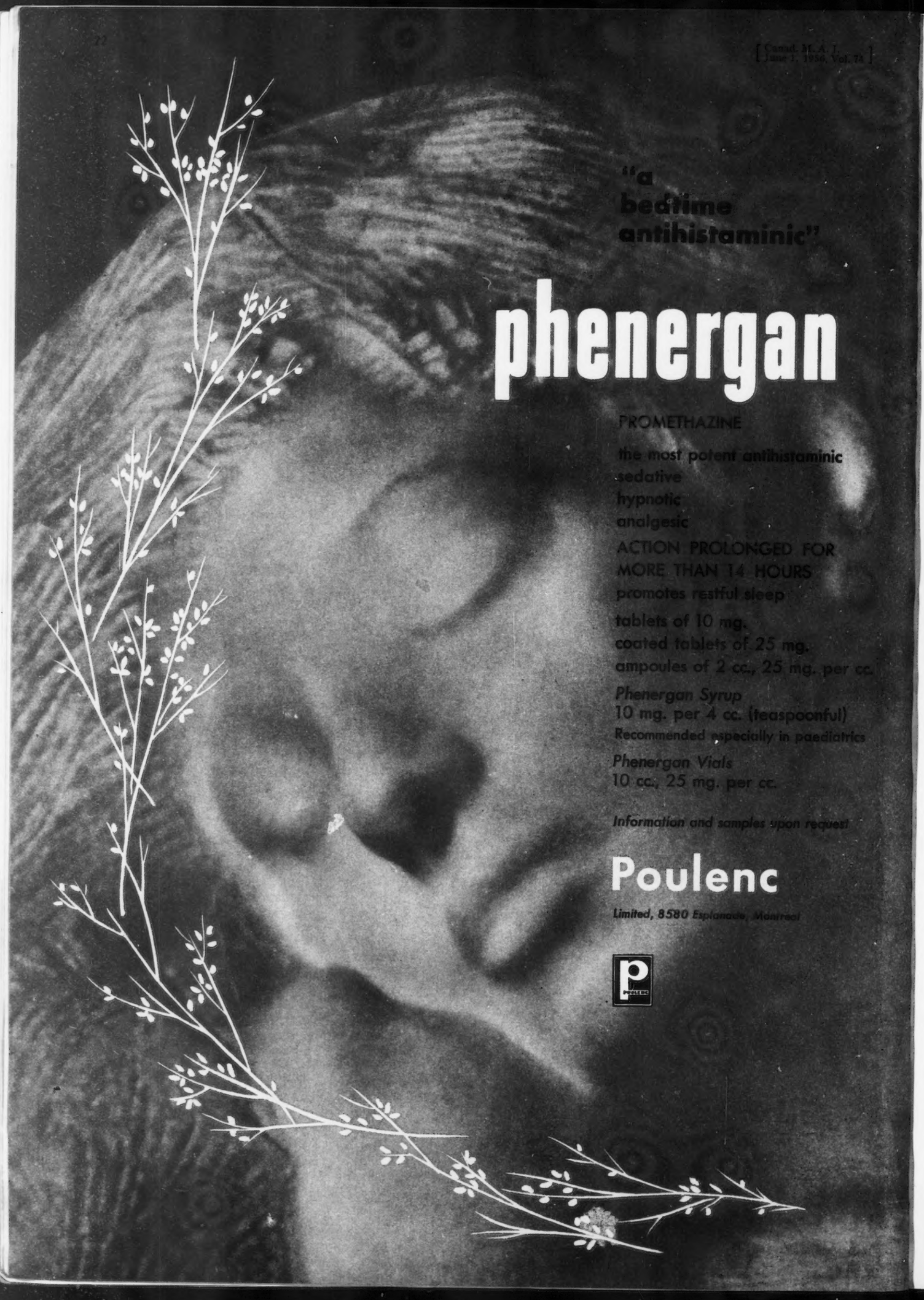

in HAY FEVER
phenergan
*"Results obtained with Phenergan
in symptomatic relief of pollen hay fever
were far superior to those obtained with
any other antihistaminic agent."
*Silbert, N. E., Ann. Allergy 10:2, May-June 1952
POULENC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the most potent antihistaminic
sedative
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promotes restful sleep
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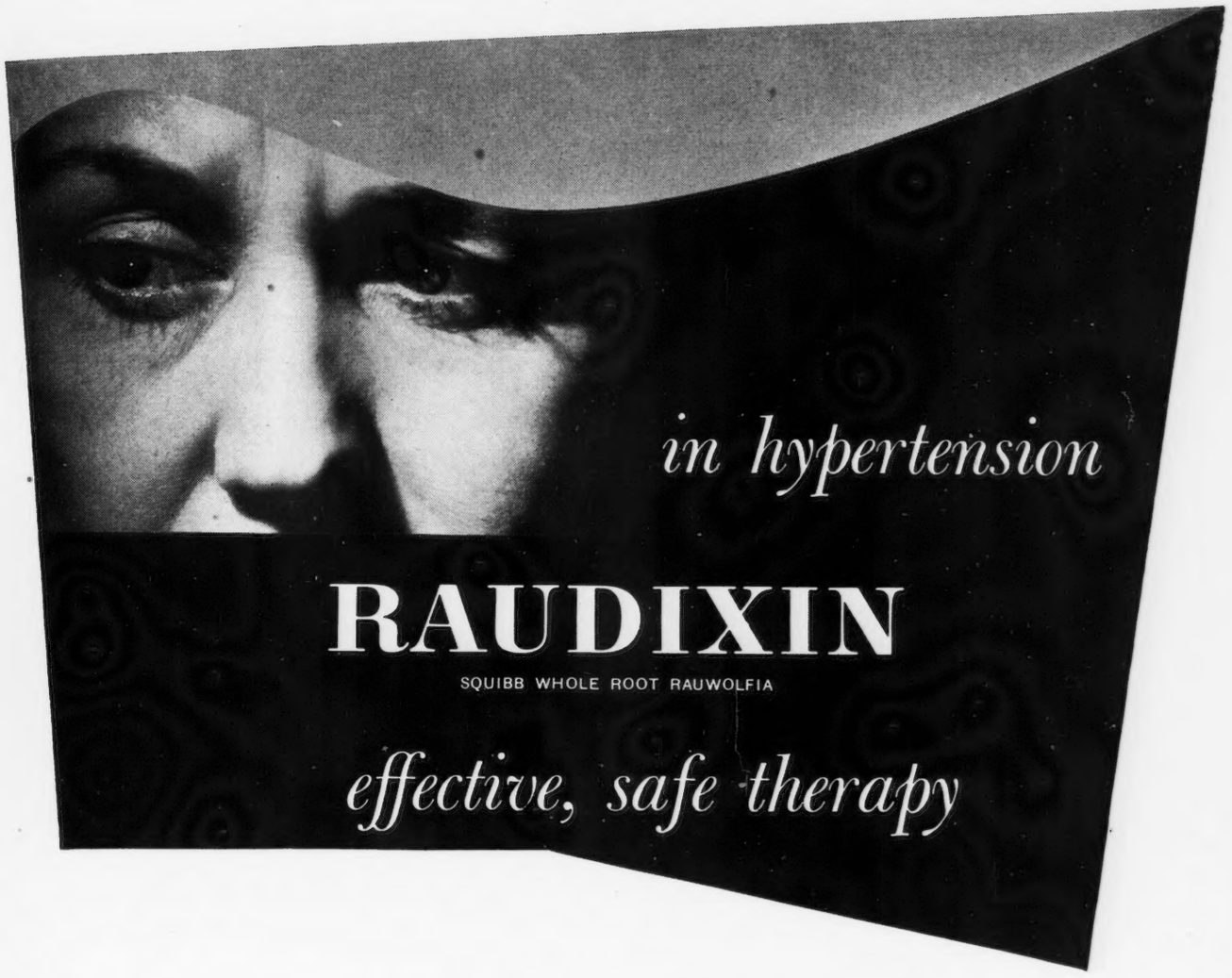

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● Raudixin may be prescribed to lower the blood pressure without the danger of a precipitous drop.

In Anxiety and Tension States a Non-Barbiturate Tranquilizing Agent.

● Raudixin is useful in patients with psychosomatic complaints or certain conditions with associated emotional overlay, such as:

headache — **insomnia**
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Dosage: 100 mg. b.i.d. initially; may be adjusted.

Supply: 50 mg. and 100 mg. tablets, bottles of 100 and 500.

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Lactofort is indicated for use in the nutritional management of pediatric patients whose appetite is persistently poor and growth consequently subnormal.

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LACTOFORT is intended *only* for the undernourished infant or child with subnormal body weight.

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Vitamin A	3750	I.U.
Vitamin D	1000	I.U
Thiamine (as mononitrate)	0.75	mg.
Riboflavin	1.25	mg.
Niacinamide	7.5	mg.
Vitamin B_{12} (crystalline)	2.5	mcg.
Folic acid	0.25	mg.
Ascorbic acid (from sodium ascorbate)	75	mg.
Pyridoxine hydrochloride	0.75	mg.
Calcium d-pantothenate	7.5	mg.
Iron ammonium citrate green (elemental iron 7.5 mg.)	50	mg.
Calcium gluconate (elemental calcium 130 mg.)	1.45	Gm.

Supplied: In 46 Gm. bottles with special Lactofort measuring spoon enclosed.

a dry powder of stable potency — odorless • tasteless • readily soluble

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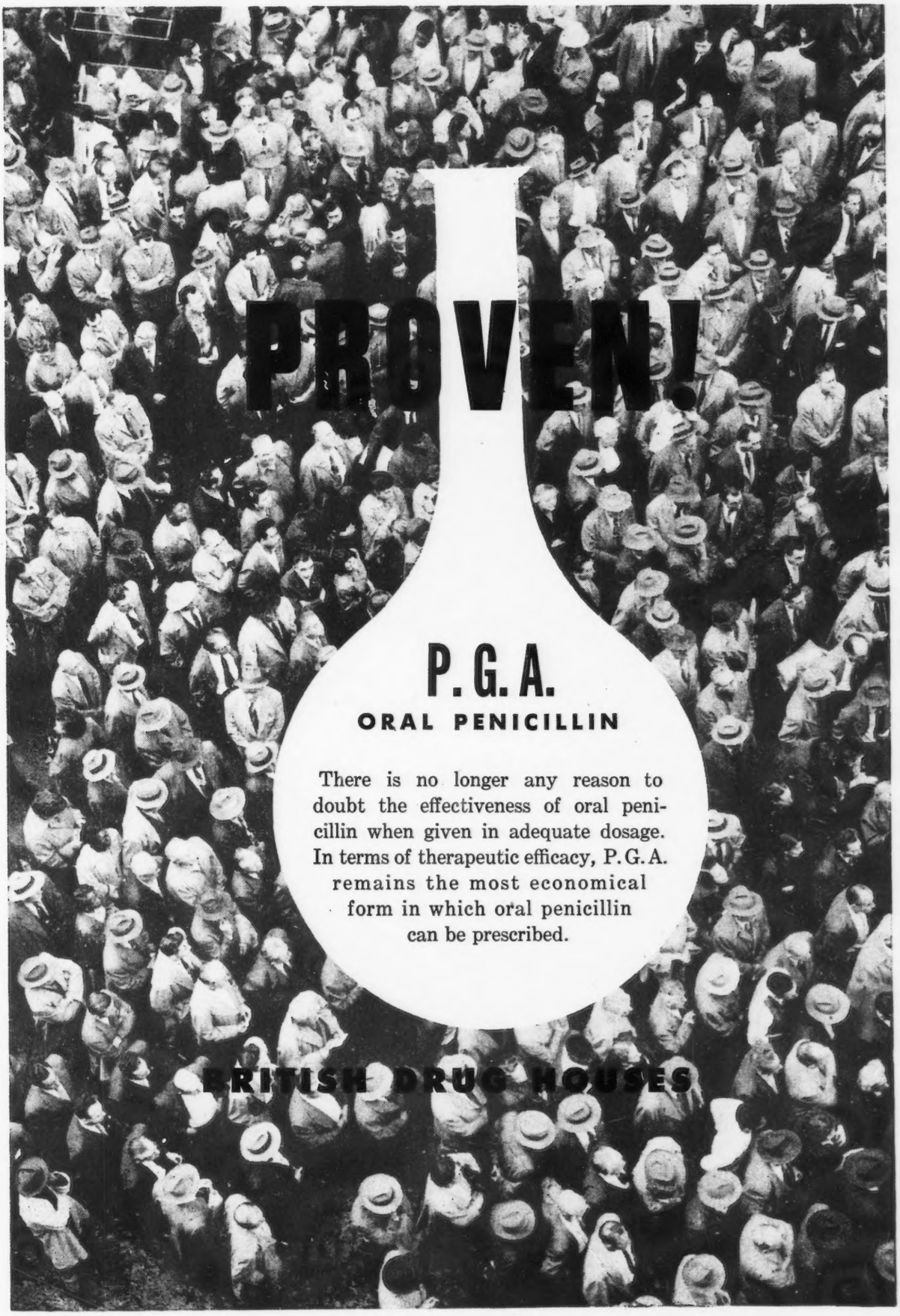
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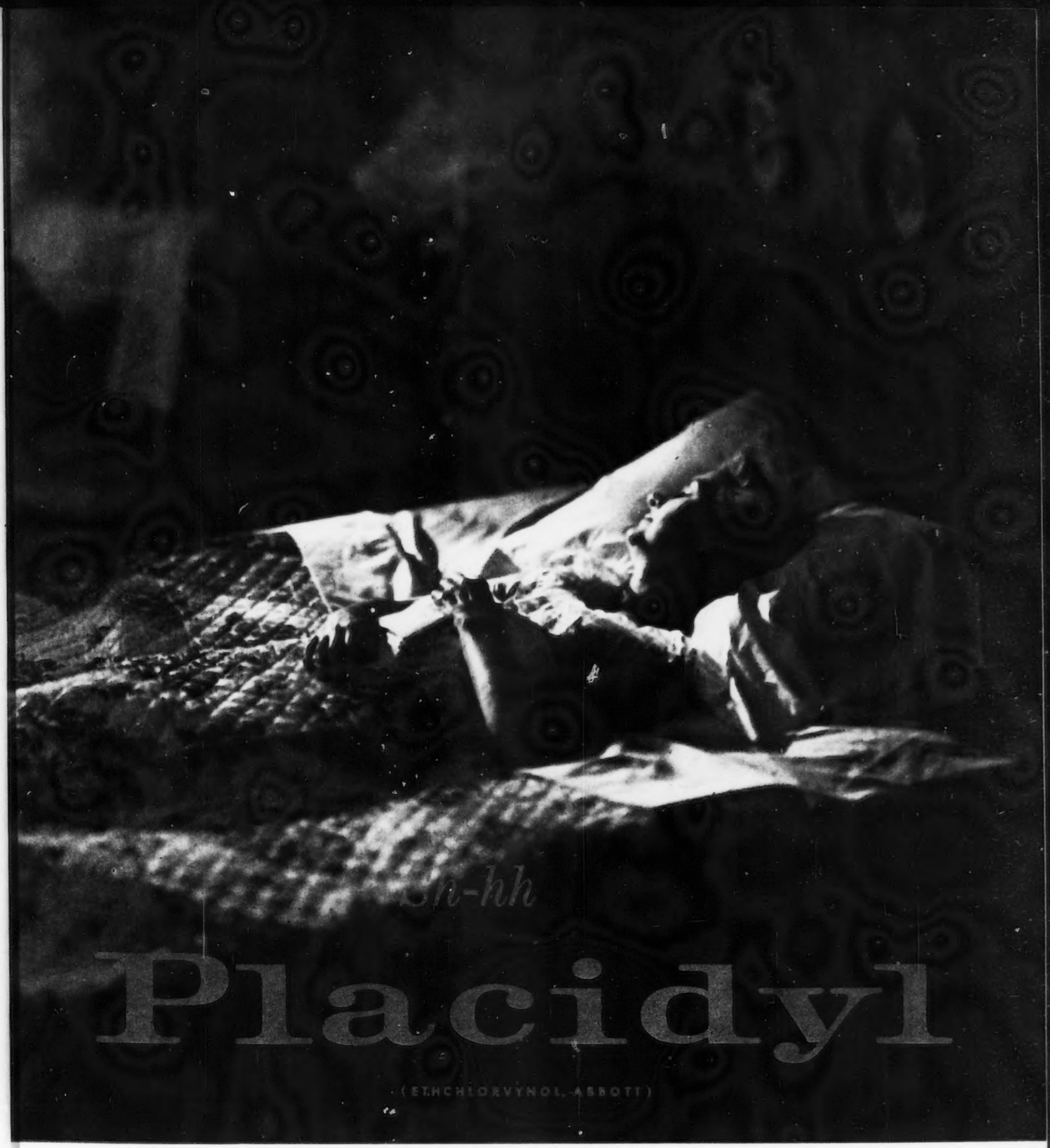

nudges your patient to sleep

This mild new nonbarbiturate hypnotic shows virtually no side effects. Doses to 1000 mg. display no effect on pulse, blood pressure, respiration, blood or urine. 500 mg. capsules, bottles of 100. Abbott

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Canad. M.A.J.
June 1st, 1956, Vol. 74

Erythromycin in treatment of pyoderma*

8/12/55

DISCHARGE SUMMARY

Patient, white female, age 39, entered hospital with a diagnosis of lymphoma, proved to be lymphosarcoma by biopsy.

Initially she was treated by X-ray radiation, adrenal cortical hormone and an antinauseant. During this regimen she developed a generalized rash which became infected. This was a drug reaction with infection due either to (1) scratching or (2) a low WBC count due to radiation. A number of boil-like lesions appeared over the body.

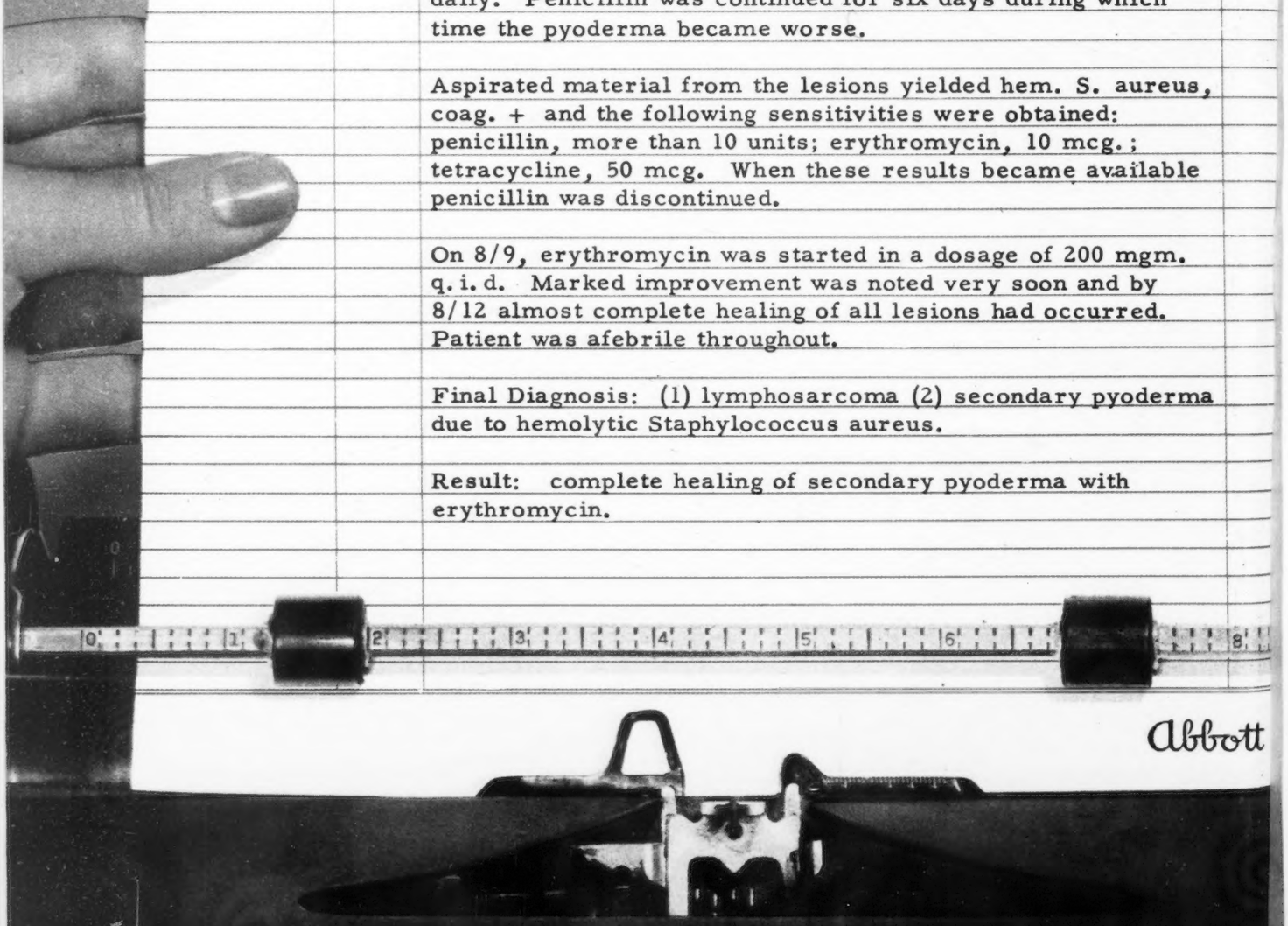
On 8/4 penicillin was started in a dosage of 600,000 units daily. Penicillin was continued for six days during which time the pyoderma became worse.

Aspirated material from the lesions yielded hem. S. aureus, coag. + and the following sensitivities were obtained: penicillin, more than 10 units; erythromycin, 10 mcg.; tetracycline, 50 mcg. When these results became available penicillin was discontinued.

On 8/9, erythromycin was started in a dosage of 200 mgm. q.i.d. Marked improvement was noted very soon and by 8/12 almost complete healing of all lesions had occurred. Patient was afebrile throughout.

Final Diagnosis: (1) lymphosarcoma (2) secondary pyoderma due to hemolytic Staphylococcus aureus.

Result: complete healing of secondary pyoderma with erythromycin.



*Communication to Abbott Laboratories

The Canadian Medical Association Journal

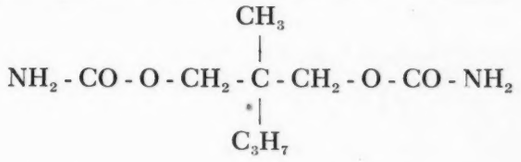
JUNE 1, 1956 • VOL. 74, NO. 11

MEPROBAMATE (EQUANIL) FOR RELIEF OF ANXIETY AND NERVOUS TENSION FROM VARIOUS CAUSES

S. E. C. TURVEY, M.D., *Vancouver, B.C.*

WHERE IS THERE A PERSON who does not hope for freedom from worry and anxiety? Since even in the ordinary vicissitudes of life many tension-producing situations arise, and under special conditions nervous strain may become intolerably severe, temporary help from medication is often desirable to render this tension less burdensome. Hence in the continued search for the perfect sedative a large series of vegetable products have been investigated, from fermented grains to the poppy seed, and finally to the root of rauwolfia, but none has approached the ideal.

One of the latest of the anxiety-relieving agents is a synthetic chemical compound, meprobamate (Equanil). Designated chemically as 2-methyl-2-n - propyl - 1:3 - propanediol dicarbamate, meprobamate was first synthesized by Ludwig and Piech[1] in 1951, with the formula



PHARMACOLOGY

A white crystalline powder with a bitter taste and faint odour, meprobamate is soluble in most organic solvents and relatively insoluble in water. The compound is stable in dilute acid and alkali, and therefore is not broken down by the gastrointestinal secretions. Meprobamate resembles mephenesin in structure but lacks the hydroxyl groups, which are rapidly oxidized within the body with resultant transience of action.

Meprobamate is described as an interneuronal blocking agent with pronounced muscle-relaxing properties.[2] In animals the compound produces a reversible paralysis of voluntary muscles without significant effects on the autonomic nervous system.[3] Internuncial circuits are inhibited without alteration of transmission at the myoneural junction or blocking of conduction in the peripheral nerves. Large therapeutic doses produce no untoward effects on blood pressure or respiration.

In cats, multineuronal reflexes are abolished without interfering with the knee jerk. Electrical recordings from the cerebral cortex and diencephalon after intravenous injection show synchronization of activity with moderate slowing of frequency and increase of voltage. The pattern is quite different from the spindling seen after administration of barbiturates. The effects are first detectable in the region of the thalamus and caudate, and the increase in voltage is greater in these areas than in the cortex.

The fate of meprobamate in the body is unknown. The kidney excretes about 10% unchanged and an additional 10% in conjugated form. Some studies have indicated that a large portion is probably conjugated to a glucuronide or similar metabolite.

PREVIOUS TRIALS

In previous clinical trials by competent observers,[4-7] meprobamate has been administered in 400 mg. tablets, usually in total daily doses of 4 to 8 (1.6 to 3.2 g.). In general, the compound acts as a mild relaxant, usually producing in the patient a tendency to natural sleep. In the intoxicated patient, meprobamate relaxes tension without stimulating the undesirable secondary response that commonly occurs after treatment with the barbiturates. In agitated individuals suffering from anxiety, depression and tension, a tendency to sleep is a particularly desirable effect. Additional sedation at night usually is unnecessary. For daytime control of nervous tension, 400 to 600 mg. every six hours causes generalized muscular relaxation, lessens nervousness, and reduces irritability and restlessness.

Somewhat similar observations have been reported after administration of promethazine, chlorpromazine, the rauwolfia derivatives and various other products.

In any group of neurotic patients, relief will occur in a certain percentage after use of almost any agent, provided the treatment is administered by a sympathetic physician. An even greater percentage will report benefit from a drug with action so mild or transient as merely to suggest an effect. What the physician needs is an agent that is harmless to the body economy,

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is without unpleasant side-actions and is not habit-forming, so that it can be administered for months or years if necessary without development of tolerance, and will be satisfactory even to a sceptical physician.

PRESENT OBSERVATIONS

Meprobamate was observed in three series of patients. The first two groups were studied at the Shadel Sanitarium, Seattle, Washington, in association with Drs. O'Hollaran, Lemere and Cunningham.

Series 1 comprised 23 acutely inebriated patients. Twenty received 800 mg. (2 tablets) meprobamate four times a day (a total daily dose of 3.2 g.). From a purely medical point of view this group was definitely improved since they were able to ingest fluids and even food remarkably well, and became mentally clear with greater rapidity than had been the experience on other occasions, during treatment with barbiturates or chlorpromazine. However, with this dose gross tremors were still evident, and the patients complained of "inner shakes" and depression. The nursing task was not significantly lessened, for the patients continued to be restless, wander about and demand drinks.

The remaining patients received 800 mg. for eight doses (16 tablets or 6.4 g.) per 24 hours for two days. Tremors, anxiety, agitation and craving for alcohol were relieved; all slept soundly during the afternoon and throughout the night. These three patients took fluids and food well and were only slightly unsteady on their feet the second day.

In *Series 2* meprobamate was used for ambulatory home management of 51 patients who had already completed 12 to 14 days of hospital treatment for acute alcoholism. Forty-eight (94%) reported subjective relief of nervous tension. These results were reported by questionnaire. In evaluating subjective findings of this nature, a few facts must be taken into consideration: (1) All of these patients had had barbiturates in some form, bromides, rauwolfia products or promethazine on previous occasions, and they should have been qualified to judge the sedative effects of the medication in the light of earlier experiences. (2) As a group, they were not susceptible to suggestion and if the drug had been ineffective they would not have been impressed merely because it was a new medication. (3) Meprobamate was administered to this group by sceptical physicians who would customarily suggest ineffectiveness of the drug by telling them, "Just try it a while; maybe it won't help." (4) The patients were told that the tablet was not a barbiturate or any other strong drug, therefore they did not expect much effect.

The patients, however, reported they had less tension, restlessness and shakiness, and felt more relaxed than in previous recoveries from alcoholic debauches; a few said the treatment made them "lazy". Although none were able to sleep as long at a time as they had hoped, all slept from 7 to 7½ hours and awoke refreshed, without drowsiness or heavy feeling. Although some said they were not as relaxed as after a barbiturate, meprobamate provided adequate calmness and enabled them to carry on their daily activities without distress.

Two patients in this group experienced mild urticaria.

Series 3 consisted of 19 patients treated with meprobamate* under my observation alone. Nine were alcoholics, 3 were addicted to pentobarbital sodium, 3 were suffering from nervous tension and tremors that had not responded to reserpine, chlorpromazine or phenobarbital, and 3 were psychoneurotics.

On 4 to 6 tablets daily (1.6 to 2.4 g.) more than 50% of the alcoholics (5 patients) had a satisfactory result. The others were not sufficiently controlled on this moderate dosage, and 2 were later controlled on reserpine. The other 2 had no relief on reserpine but were moderately relieved on phenobarbital.

Of the 3 drug addicts 2 were satisfactorily controlled on 6 to 8 tablets daily. The craving of one, however, had never been satisfied previously by anything but pentobarbital sodium.

About 60% of the psychoneurotics and the patients with tension and tremors were satisfactorily relieved on a total daily dosage of 4 to 6 tablets (1.6 to 2.4 g.). For intractable insomnia, addition of ½ grain phenobarbital to the dose at 6 and 11 p.m. usually provided adequate sleep. No side-effects occurred in this group.

Three of the alcoholic patients observed in this study received meprobamate during treatment with tetraethylthiuram disulfide. No ill effects from the use of such combined therapy were seen.

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*Equanil (meprobamate) was supplied by Wyeth Laboratories.

SUMMARY AND CONCLUSIONS

Meprobamate (Equanil) was used, in three separate series, for treatment of a total of 93 patients, including 83 alcoholics, 3 drug addicts, 3 patients with nervous tension and tremors, and 4 psychoneurotics. Results were satisfactory in the great majority on the moderate dosage initially recommended. With increase of the dose in some of the resistant cases, especially among the alcoholics, the effectiveness of treatment was enhanced. There seems no criterion for selection of patients except clinical trial.

A safe, not habit-forming relaxant, meprobamate (Equanil) is useful for relief of anxiety, tension and depression, particularly after episodes of acute alcoholism.

The results of this study indicate that Equanil is more satisfactory for relaxation of the alcoholic patient than the barbiturates. Used simultaneously with tetraethylthiuram disulfide, meprobamate did not interfere with treatment.

Except for urticaria in 2 patients in Series 2, no side-effects were reported.

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RÉSUMÉ

Le Meprobamate (Equanil) fut employé, en 3 séries distinctes, pour le traitement d'un groupe de 93 malades, comprenant 83 alcooliques, 3 toxicomanes, 3 malades souffrant de tension nerveuse et de tremblements, et 4 névropathes. Dans la grande majorité des cas, on obtint des résultats satisfaisants avec la dose modérée prescrite (1.6 à 3.2 grammes). En augmentant la dose pour quelques-uns des cas réfractaires, surtout parmi les alcooliques, l'efficacité du traitement fut augmentée. Il ne semble pas y avoir de règle spéciale pour le choix des patients, sauf l'essai clinique.

Le Meprobamate (Equanil), relâchant sûr sans risque d'accoutumance, est utile pour le soulagement de l'angoisse, de la tension et de la dépression, particulièrement à la suite de périodes d'alcoolisme aiguë.

Les conclusions de cette étude montrent que Equanil donne de meilleurs résultats que les barbituriques pour la détente des alcooliques. Employé simultanément avec le bisulfure de tetraethylthiuram, le Meprobamate n'entrave pas le traitement.

On ne rapporta pas d'effets secondaires, à l'exception d'urticaire chez 2 malades. M.R.D.

FURTHER CLINICAL STUDIES OF THYROID AND SALIVARY GLAND FUNCTION WITH RADIOIODINE*

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RADIOIODINE TESTS of thyroid function are based on the well-established ability of the thyroid gland to concentrate iodide ion given either orally or intravenously, to convert it more or less rapidly into thyroxin and finally to secrete thyroxin into the blood stream. Although each radioiodine test used today is designed to measure thyroid activity, it is obvious that no one test can measure all aspects of thyroid function. At best, each test will measure the rate at which some phase of the iodine cycle takes place. The most commonly used radioiodine pick-up tests, for example, measure in the first instance the ability of the thyroid gland to trap iodide ion, the tests being made a few hours after the administration of a tracer dose. On the other hand, the usual 24-hour pick-up test will in addition measure the ability of the thyroid gland to store iodine in the form of thyroxin.

Uptake or pick-up tests do not, however, measure the rate of secretion of thyroxin into the blood stream, and since the uptake does not always correlate with the clinical condition of the patient, it seems clear that the radioiodine uptake and the output of hormone do not always bear a constant relation. A number of tests are therefore designed to measure the rate of output of thyroid hormone. Still other tests are concerned with the amount of protein-bound radioiodine in the plasma. For example, the so-called iodine conversion ratio measures the proportion of the total plasma radioactivity in the organic fraction at 24 hours. It is our experience and the experience of others that this test of thyroid function correlates better with the clinical condition of the patient than does the 24-hour pick-up test.[1-3]

*From the Department of Medical Research, Hamilton College, McMaster University, Hamilton, Ont. Read by Dr. Jaimet at the United Nations Meeting in Geneva, during the Conference for the Peaceful Uses of Atomic Energy, in August 1955.

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Although pick-up and conversion ratio tests are approximately 85 and 95% accurate respectively in the diagnosis of hyperthyroidism, both tests are disappointing in the diagnosis of hypothyroidism.[2, 3] It is obvious therefore that these tests and slight variations of them do not give the full story. It is well known, of course, that the pituitary secretion of the thyroid stimulating hormone (TSH) plays an important role in controlling the level of thyroxin in the plasma. Jeffries *et al.*,[4] recognizing the need for a better test for hypothyroidism, investigated the effect of TSH on the radioiodine pick-up test in euthyroid, hypothyroid and hyperthyroid patients. It was found that the pick-up did not increase for primary hypothyroid patients after a dose of TSH as it did for others. This test has proved to be very useful in the diagnosis of hypothyroidism.

There are, however, still other phases of the iodine cycle which appear to have a bearing on thyroid function. Recent biochemical and clinical studies indicate that the salivary glands are concerned in the iodine cycle in the body. For example, the discovery of Fawcett and Kirkwood[5, 6] of our University that the thyroid enzyme, tyrosine iodinase, responsible for the iodination of tyrosine to monoiodotyrosine is also present in relatively high concentrations in the salivary glands, indicates a direct relationship between the two gland systems. Their further studies with labelled diiodotyrosine give positive evidence that the salivary glands may be responsible for the degradation of thyroxin in the body and the recycling of the iodine to the thyroid gland as iodide ion.[7] It has, of course, been known that the salivary glands concentrate iodide ion into the saliva, the concentration in the saliva being about 30 times that of the blood plasma. But these results taken together indicated a definite relationship between thyroid and salivary gland function and suggested to us that radioiodine tests on the saliva of euthyroid, hyperthyroid and hypothyroid patients might correlate with and supplement conventional thyroid tests.

Our first results obtained on 76 patients reported earlier[8, 9] showed a remarkable correlation between the radioiodine secreted by the salivary glands and thyroid function. For example, the saliva radioactivity varied from 83 counts per minute (c.p.m.), 3 c.c. samples, for a hyperthyroid patient to 24,000 c.p.m. for a hypothyroid patient, 24 hours after administration of 50 μc. of I^{131}, the average values being 493, 2,393, and 12,172 for the hyperthyroid, euthyroid and hypothyroid groups respectively. When the saliva activity (S) was compared with that in the blood plasma (P) (S-P ratio), an equally good correlation with thyroid function was obtained. However, a very much better indication of thyroid function was obtained when we compared the saliva activity in relation to the protein-bound iodine (PBI) activity in the plasma (S-PBI ratio). An excellent diagnostic test for thyroid disorders was therefore indicated, as well as clinical evidence for the salivary-thyroid gland relationship. It should be pointed out that Freinkel and Ingbar[10] reported no correlation between 30-min. saliva-plasma activity ratios and thyroid function. The difference between the 30-min. and the 24-hour saliva tests has not been fully explained.[8, 10]

Radioiodine saliva tests have now been carried out on an additional 350 patients to evaluate their usefulness more fully. Also, saliva tests have been made on patients receiving labelled L-thyroxin tracer in order that the role played by the salivary glands in the iodine cycle might be further elucidated. The results of these investigations are reported in this paper.

EXPERIMENTAL OBSERVATIONS

Details of the radioiodine pick-up, conversion ratio and saliva tests as performed by us have previously been described.[2, 8] The radioiodine pick-up and conversion ratios are measured with especially designed scintillation counters 24 hours after the administration of a 50 μc. dose of radioiodine. In the latter test the protein-bound fraction of a 3 c.c. aliquot of blood plasma was precipitated with trichloracetic acid, washed free of serum, redissolved with sodium hydroxide and finally diluted to the original 3 c.c. volume. The radioiodine activity of the 3 c.c. sample was then compared with the activity of a 3 c.c. aliquot of the original plasma, the ratio of activities being called "conversion ratio."[1] The sample activities were measured wet in plastic dishes mounted over a crystal detector well shielded by lead. Finally, 3 c.c. aliquots of saliva obtained from the patients by simple expectoration 24 hours after administration of tracer doses of radioiodine were measured into plastic dishes and the activity was determined as before.

The samples were counted with the scintillation counter for five minutes. With this counting time the natural background of the counter, 80 to 100 c.p.m., could be determined to 5%. Since the scintillation counters were used to count gamma rays with wet samples, self-absorption problems were negligible. Further, there was no evidence of radioiodine losses in the sample dishes even on long standing.

RESULTS

Since our last report,[9] 350 new patients have been investigated to compare the results of I^{131}

tests. Seventy of these were hyperthyroid, 40 were hypothyroid, 20 were having tests of progress at various times after I^{131} therapy, and the balance were normal controls or euthyroids. The diagnosis in each case was first based on clinical assessment, radioiodine pick-up and conversion ratio tests. Tables II and III give the results obtained for a representative group of hyperthyroid and hypothyroid patients respectively. The total number of patients was then listed in groups in order of magnitude of saliva-PBI activity ratio, or according to thyroid activity, and the tables include the data of every second or third patient. The data are therefore truly representative. Table I includes results obtained for a group of normal subjects for comparison. The second and third columns of the tables give the 24-hour radioiodine pick-up and conversion ratio tests. The fourth, fifth and sixth columns give the ratio of the saliva activity to plasma-iodide ion activity (S-iodide ion ratio), the saliva activity, and the ratio of the saliva activity to activity of protein-bound iodine in the plasma (S-PBI ratio) respectively.

In a number of cases the conventional radioiodine tests did not agree with each other, in which case the diagnosis was decided on the basis of clinical symptoms. In the case of the hypothyroids, the diagnosis was much more difficult because conversion ratio and pick-up tests are often not indicative. However, when the patients are listed according to saliva activity and in particular according to the saliva-PBI activity ratio (as in Tables I, II and III), it is found that saliva-PBI activity ratios above 400 and ranging to 1,900 included all patients with either low pick-up or a low conversion ratio and all who showed clinical symptoms suggestive of hypothyroidism. Furthermore, a number of patients whose saliva gave a "hypothyroid" test and whose clinical condition was in some doubt were tested further using Jeffries' TSH (thyroid stimulating hormone) test for obscure hypothyroidism.[4] Each case suspected by saliva test was found to be hypothyroid with the TSH test. The results therefore confirm our preliminary work reported earlier that the saliva-PBI activity ratio is an excellent index of thyroid function, and this is particularly true for hypothyroidism. In general, the saliva activities 24 hours after the administration of a tracer dose of radioiodine are low, intermediate and high in hyperthyroidism, euthyroidism and hypothyroidism respectively; the saliva-PBI activity ratio, which appears to be a better index of thyroid function, ranges from 0.14 to 44 for hyperthyroids, from 150 to 250 for normal subjects and from 400 to over 1,900 for hypothyroids; the borderline-ranges between the three groups, from 50 to 150 and from 250 to 400 respectively, probably include in addition to euthyroids, patients who are mildly hyperthyroid and hypothyroid respectively.

The saliva tests have been found by us to be a most useful aid in the diagnosis of thyroid disorders. Frequently these tests have indicated hypothyroid or hyperthyroid states when other tests indicated normal function contrary to clinical signs or symptoms. Too, the S-PBI test seems to represent clinical progress more accurately than other tests of progress after treatment.

I^{131} Labelled L-Thyroxin Tests

In the normal radioiodine tracer tests the radioiodine is given in the form of inorganic iodine, which is removed from the circulation by the thyroid gland and then returned to the blood stream in the form of labelled hormone. In two experiments, normal subjects were given tracer radioiodine in the form of I^{131} labelled L-thyroxin direct by intravenous injection. To follow the circulation and degradation of L-thyroxin, 3 c.c. samples of blood and saliva were taken and the percent total pick-up in the thyroid determined at intervals of time. Results obtained approximately 2, 20 and 140 hours after the administration of I^{131} labelled L-thyroxin are shown in Table IV. Many additional pick-up and saliva tests were made during the period of the experiment. The percent total pick-up in the thyroid rose for the first 100 hours and then appeared to level off at 9 and 11% for patients 1 and 2 respectively. After 140 hours, about 10% of the activity in the blood was in the form of inorganic iodine as determined by precipitation with trichloracetic acid.

Some indication of the rate of hormone turnover can be deduced from the decrease in PBI activity in the blood with time. After the first 20 hours, the PBI activity is seen to fall off at about 16% per day. Most important from the point of view of our saliva tests is the low saliva-PBI activity ratio which is seen to be of the order of 0.5 to 0.6 for normal subjects. Recently Freinkel and Ingbar[11] performed sim-

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ilar tests in subjects with diverse states of thyroidal activity and report 24-hour saliva-PBI activity ratios of from 0.08 to 1.27. Although this variation between patients with diverse thyroid activities is in itself indicative of some relationship between thyroid and salivary gland function, it is nevertheless clear that the very high saliva activities and the high saliva-PBI activity ratios obtained for patients receiving inorganic iodine tracer (see Tables I-III) are largely due to the ability of the salivary glands to trap and concentrate iodide ion into the saliva. Only the patients with very active Graves' disease have saliva-PBI ratios as low as or lower than 0.5.

DISCUSSION

Value and Significance of Saliva Tests

Saliva tests have been made on over 400 patients with varied thyroid activity and it is quite clear that the saliva activity and the saliva-PBI activity ratio obtained 24 hours after the administration of a tracer dose of radioiodine as iodide ion is a remarkably good index of thyroid function. The question arises as to the significance of the saliva tests and the role played by the salivary glands in the iodine cycle. It is well known that iodide ion is removed from circulation by the salivary glands and concentrated into the saliva.[12-14] Therefore, regardless of whether they also degrade thyroxin as suggested by Fawcett and Kirkwood,[6, 7] the majority of the iodide concentrated must arise from the inorganic iodide in the blood. Thus, in so far as the salivary gland function is not altered in any way, the saliva activity tests will reflect the iodide ion level in the blood stream. Also, in a general way, it will be true as suggested by others[11] that there will be a more or less high and low iodide ion level in the blood 24 hours after a tracer dose of iodide ion for hypothyroids and hyperthyroids respectively, even though this picture is complicated by such factors as thyroid gland "hold-up" of iodine which depends on the size and nature of the gland. It is apparent, however, from our results that the degree of functional activity of the salivary gland is altered and the accurate saliva tests for thyroid function are reflecting a connection between these two gland systems. It is seen from Tables I, II and III, column 4, that the saliva-plasma iodide ratio, which is a measure of one aspect of salivary gland function, is

TABLE I.

TWENTY-FOUR HOUR RADIOIODINE TESTS OF SALIVARY AND THYROID FUNCTION* NORMAL SUBJECTS (EUTHYROID)

Patient No.	*Total pick-up %*	*Conversion ratio %*	*Saliva-iodide ion[1] activity ratio*	*Saliva activity c.p.m./3 c.c.*	*Saliva-PBI[2] activity ratio*
19	28	11	18	1,123	160
28	23	18	37	3,726	170
65	18	17	35	2,306	177
22	26	13	26	1,601	178
34	31	23	59	4,180	199
30	32	19	47	1,990	199
20	35	16	43	1,878	235
Averages	28	17	38	2,393	188

*All tests made 24 hours after oral administration of a 50-microcurie dose of radioiodine as iodide ion.
[1]Refers to iodide ion activity in 3 c.c. plasma.
[2]Refers to protein-bound iodine activity in 3 c.c. plasma.

TABLE II.

TWENTY-FOUR HOUR RADIOIODINE TESTS OF SALIVARY AND THYROID FUNCTION IN PATIENTS WITH DIAGNOSIS OF HYPERTHYROIDISM*

Patient No.	*Total pick-up %*	*Conversion ratio %*	*Saliva-iodide ion[1] activity ratio*	*Saliva activity c.p.m./3 c.c.*	*Saliva-PBI[2] activity ratio*
86	82	81	—	71	0.14
237	60	98	21.0	496	0.50
260	74	96	15.0	216	0.70
230	73	80	3.7	179	1.00
215	64	64	1.9	81	1.10
221	61	76	3.7	136	1.20
137	83	97	81.0	163	1.60
216	65	79	7.8	238	2.00
102	78	95	46.0	370	2.60
292	83	67	6.5	295	3.20
105	71	92	41.0	205	3.80
194	53	91	46.0	969	5.40
147	72	78	24.0	289	6.90
181	63	81	34.0	553	8.30
206	64	66	25.0	150	12.50
140	39	50	18.0	513	17.00
192	44	50	25.0	343	24.60
212	52	66	59.0	1,429	29.80
177	8	14	5.9	252	36.00
113	37	31	19.0	660	44.00
Averages	61	73	25.4	380	10.10

*All tests made 24 hours after oral administration of a 50-microcurie dose of radioiodine as iodide ion.
[1]Refers to iodide ion activity in 3 c.c. plasma.
[2]Refers to protein-bound iodine activity in 3 c.c. plasma.

TABLE III.

TWENTY-FOUR HOUR RADIOIODINE TESTS OF SALIVARY AND THYROID FUNCTION IN PATIENTS WITH DIAGNOSIS OF HYPOTHYROIDISM*

Patient No.	*Total pick-up %*	*Conversion ratio %*	*Saliva-iodide ion[1] activity ratio*	*Saliva activity c.p.m./3 c.c.*	*Saliva-PBI[2] activity ratio*
186	18.0	11.0	52	4,950	413
233	8.5	8.9	42	7,760	431
285	22.0	7.7	38	19,180	456
244	2.0	6.2	34	2,547	509
256	19.0	7.4	43	11,365	541
289	13.0	9.6	61	13,590	566
172	17.0	14.0	100	14,100	613
187	2.0	16.0	124	10,500	657
247	22.0	10.0	82	16,330	742
218	19.0	13.0	123	14,420	849
255	6.3	3.2	28	6,900	862
116	8.0	13.0	148	34,100	971
303	20.0	6.8	81	24,605	1,121
240	8.7	6.8	94	33,600	1,300
301	7.3	5.5	112	76,000	1,900
Averages	13.9	9.4	77	19,333	795

*All tests made 24 hours after oral administration of a 50-microcurie dose of radioiodine as iodide ion.
[1]Refers to iodide ion activity in 3 c.c. plasma.
[2]Refers to protein-bound iodine activity in 3 c.c. plasma.

far from constant. There is considerable overlapping of this ratio between groups of patients, and the average value of the ratio for hypothyroids is about double that for normals. It is, of course, noted that in normals and hypothyroids both the saliva and plasma iodide samples are high in activity and can be determined accurately, whereas for hyperthyroids the iodide ion level in the plasma is often low and *in vitro* experiments depending on the redox potential. In the thyroid gland its role is obviously a synthetic one and, since there is no evidence for the synthesis of organically bound iodine in the salivary glands, they have suggested the salivary glands as a seat of the deiodination process which is known to take place in the body. Recently they published data which provide direct evidence that the salivary

TABLE IV.

RADIOIODINE LABELLED L-THYROXIN TRACER TESTS*—NORMAL SUBJECTS

		Plasma						
Subject	*Elapsed time—hours*	*Total activity c.p.m./3 c.c.*	*PBI activity c.p.m./3 c.c.*	*Total pick-up %*	*Conversion ratio %*	*Saliva-iodide ion[1] activity ratio*	*Saliva activity c.p.m./3 c.c.*	*Saliva-PBI[2] activity ratio*
1	2.3	4,587	4,197	0.6	92	7.3	2,865	0.68
	20.3	2,355	2,202	5.2	94	7.2	1,095	0.50
	139.3	708	608	9.0	91	4.4	294	0.46
2	2.0	34,515	34,477	1.5	100	—	6,930	0.20
	20.0	9,062	8,941	5.7	99	—	4,150	0.46
	139.0	3,637	3,283	11.0	90	5.5	1,950	0.59

*Subjects 1 and 2 given intravenous injections of 50 microcuries and 200 microcuries of I^{131} labelled L-thyroxin respectively.
[1]Refers to iodide ion activity in 3 c.c. plasma.
[2]Refers to protein-bound iodine activity in 3 c.c. plasma.

the saliva-iodide ratio is not always so significant. It seems clear therefore that the degree with which the salivary glands concentrate iodide ion from the blood stream through to the saliva varies widely from patient to patient within each group and is in general altered with thyroid activity. The saliva tests of thyroid function must therefore reflect a connection between thyroid and salivary glands as well as iodide ion level in the blood. Saliva flow rates will, of course, have a bearing on the saliva tests. For example, high flow rates might be expected to show low iodide ion activity and vice versa. However, the saliva flow rate must reflect an important aspect of the function of the salivary glands which, like their ability to concentrate iodide ion, might well be altered by thyroid gland disorders.

Certainly, the most direct evidence of a connection between the salivary and thyroid glands is the presence of the thyroid enzyme, tyrosine iodinase, in the salivary glands in relatively high concentration and in large amounts first demonstrated by Fawcett and Kirkwood[6] in our laboratories. They have shown that this enzyme will catalyze the synthesis of monoiodotyrosine (MIT) as well as its deiodination in controlled glands do function in the metabolism of organic iodide[8] and preliminary results in our laboratories indicate for the first time the existence of organically bound iodine in the saliva.[15] If the salivary glands are a seat of deiodination of thyroxin, alterations in salivary gland activity, such as our saliva tests reflect, are to be expected. It is clear also that, in the saliva tests reported, any iodide in the saliva due to degradation of thyroxin would in most cases be masked by the larger amount of iodide ion normally concentrated from the blood into the saliva, since the degradation rate is only between 10 and 15% per day.

Although perhaps less direct, there is much additional evidence in the literature suggesting a connection between the salivary and thyroid glands. For example, Hämmerli[16] has reported that submaxillary weight increases as the thyroid weight in goitre patients and Albright[17] has recently reported hypertrophy of the salivary glands during the treatment of myxœdema with triiodothyronine. Also, Rawson[18] has reported swelling of the submaxillary and parotid salivary glands in a patient treated with thiouracil. This patient showed a marked decrease in thyroid

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function when under treatment with thiouracil, and one of her parotid glands underwent permanent atrophy. These results are similar to those of Leblond and Grad[19] and Arvey *et al.*,[20] who showed that thyroidectomy and treatment with thiourea both result in atrophy of the submaxillary salivary glands of rats.

There are many clinical conditions with varying degrees of hypothyroid or hyperthyroid activity. Each I^{131} tracer test adds something to our knowledge of thyroid function. Any clinician-isotopologist, however, will admit that each test devised, and often a combination of two or more, will not infrequently fail to clearly point up the thyroid state to his satisfaction. It is to be noted, therefore, that we do not rely on the S-PBI test alone to indicate final diagnosis; we will continue to do our other tests and we will add the more recent "two-hour pick-up" and the "triiodothyronine suppression" as well as the "TSH" tests to our "battery" when indicated. As clinicians and scientists, however, we are impressed with the aid received from the S-PBI test, especially since it requires so little more of the patients' time, no extra visits, and is simply performed in any laboratory doing plasma radioiodine measurements.

SUMMARY

Radioiodine saliva tests for thyroid function have been evaluated on over 400 patients. Not only was the S-PBI ratio test found to be almost 100% accurate, but in many cases where other radioiodine tests gave inconclusive results the S-PBI test gave a clear-cut answer more consistent with the final clinical diagnosis. Advantages of the S-PBI test for thyroid function appear as follows: (1) It is equally accurate with radioiodine pick-up and conversion ratio tests for hyperthyroids. (2) It gives an accurate indication of hypothyroidism, whereas other tests give disappointing results (thyroid stimulating hormone (TSH) test excepted). (3) It seems to follow clinical symptoms more closely in patients under treatment with radioiodine, propyl thiouracil and other therapy.

Finally, the excellent correlation between saliva tests and thyroid function provides strong clinical evidence for a connection between the salivary and thyroid gland systems and supports the evidence of Fawcett and Kirkwood of our University that the salivary glands play an important role in the iodine cycle in the body—perhaps in the degradation of organically bound iodine.

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WILLIAM HEBERDEN, M.D., ON "APOPLEXIES, SUDDENLY, PLANET-STRUCK, LETHARGIES AND PALSIES"

"The yearly sum of the deaths ranged under the heads of apoplexies, suddenly, planet-struck, lethargies, and palsies, fluctuates without any constant increase or decrease, till the beginning of the present century [18th]: from which time this sum has been perpetually increasing, so that the middle proportion of it for every ten years to the total of the burials, constantly exceeds that of the preceding ten years. In the last ten years this increase has been the greatest of all, nearly one fourth more having died of these distempers, than there did at a medium in any other successive ten years; and a double proportion died of them in these ten years to what there did at an average in the same space of time before the beginning of this century. Is this difference only an apparent one, arising from the placing of some deaths under these in the later bills, which formerly came under other articles? There seems no reason for such a suspicion and the gradual increase of these sums is an argument against it. If the increase be real, is it owing to any alteration in our manners or diet? And what is that alteration?"—William Heberden, M.D., from his preface to "A Collection of the Yearly Bills of Mortality from 1657 to 1758 Inclusive". Printed in London in 1759 by Halkett and Laing for A. Millar.

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THE SIGNIFICANCE OF GLUCAGON

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GLUCAGON is a general term which has been adopted to characterize a factor causing hyperglycæmia and originating in the pancreas. Such a factor is frequently present in crude and even in refined insulin preparations.

Various aspects of physical, chemical and physiological properties of extracted glucagon have been reviewed recently.[1-7] To summarize from these, extracted glucagon in highly potent purified (crystalline) forms has been found to be a zinc-free protein of low molecular weight with structural elements sufficiently different from those of glucagon-free insulin to indicate that it is neither a precursor nor a degradation product of insulin. The outstanding physiological action of glucagon, the one by which its potency is assayed in biological media, is its ability to accelerate the breakdown of glycogen in intact liver cells to glucose by activation of liver phosphorylase. While glucagon shares this property with epinephrine, it differs from epinephrine in action in that it has no detected effects on the breakdown of muscle glycogen or on the blood pressure.

Glucagon is inactivated or removed by the liver in physiological systems within minutes after its release into the blood stream. When injected into extrahepatic tissues, its hyperglycæmic action is largely lost. When hypoglycæmic blood is passed through the pancreas of a normal dog, the dog is observed to release a hyperglycæmic factor, insulin being released when the blood entering the pancreas is hyperglycæmic. Thus the hyperglycæmic factor and insulin act synergistically to stabilize the blood sugar level.

The statements made in the above summary are subject to certain reservations indicated below. In the first place, the name *glucagon* has been used very loosely in the literature. Originally glucagon was defined as a substance which could be extracted by water from beef pancreas, cat's muscle and yeast, and which produced its greatest hyperglycæmic effect several hours after its subcutaneous injection into depancreatized dogs.[8] Many glucagon and insulin extractions are now made using acid alcohol,[9] glucagon activity being observed only in extracts from the pancreas and in some cases from the gastrointestinal mucosa. These alcoholic extracts have not proven effective in raising the blood sugar level in depancreatized dogs not treated with insulin, presumably because such animals have little or no liver glycogen to produce lysis.

In modern usage the term glucagon has been used to designate both the *secreted* and the *extracted* hyperglycæmic factors of the pancreas. However, there is evidence that even these factors are not identical in their action.[10] While each of the two extracted crystalline proteins described in the literature as highly purified glucagon differs from insulin in its structural elements,[5, 11] each also differs significantly in this regard from the other.

It is clear that, with the existence of such basic difficulties in characterizing glucagon, some rule of terminology must be adopted to indicate the origin of different preparations. Following the discovery of insulin, a similar problem was overcome by appending the name of the laboratory or extraction centre to marketed preparations (e.g., Insulin-Toronto, Insulin-Novo, Insulin-Squibb). A similar nomenclature will be adopted here to indicate the source of different preparations of purified glucagon (e.g., glucagon-Lilly, glucagon-Karlsburg). Preparations of unspecified purity will be simply referred to as *extracted glucagon*, the term *glucagon* being reserved for the substance secreted into the portal vein which causes the breakdown of liver glycogen to form glucose.

There has been no clear-cut agreement as to the site of origin of glucagon *within* the pancreas, doubtless in part because of the above-mentioned confusion regarding terminology. The data of many workers indicate the alpha cells of the islets of Langerhans as a probable site of origin.[3, 12, 13] This view has been challenged by Volk, Lazarus and Goldner,[7] whose basic observation is that hyperglycæmic activity persists in pancreatic extracts following destruction of the alpha cells of rabbits and dogs by cobaltous chloride. It now appears that cobaltous chloride may cause degranulation without necrosis of the alpha cells of rabbits,[14] and that even the degranulation may not be associated with a fall in the potency of the extracted glucagon.[15]

Independent checks on whether cobaltous chloride destroys the alpha cells in dogs and rabbits are obviously needed. Recent measure-

ments on the normal distribution of alpha cells and of extractable glucagon in the same dog pancreas are now admitted by Lazarus as indirect evidence that the alpha cells represent a source of glucagon.[16]

Mayer[13] has suggested that the term "Nesocrine" (Greek: νῆσος = island) be used to circumvent the difficulties involved in naming glucagon after any *one* of its properties. Unfortunately the proposed new name is also involved with the assumption that the hyperglycæmic factor is produced and secreted by cells in the islets of Langerhans. The abdominal lymph nodes have been indicated recently as a site of origin of such a factor.[17]

With this shifting background of fact and hypothesis in mind, an attempt will be made to draw together the results of studies on glucagon and extracted glucagon as they relate to normal and pathological states in man.

Responses to Glucagon in Non-Diabetics

Accelerated production of glucose in the splanchnic area of man following administration of extracted glucagon has been demonstrated by hepatic venous catheterization.[15] Thus the view is supported that man's response to the hyperglycæmic and glycogenolytic actions of extracted glucagon corresponds to that seen in other species of mammals.

If glucagon represents a physiological factor in the metabolism of man, its function or functions should be demonstrable. Based on blood transfer studies between normal human subjects during muscular exercise and in the course of glucose tolerance tests, Buerger[19] has proposed that glucagon acts with insulin to cause carbohydrate stored in the liver to be transferred to the muscles and other peripheral tissues at times when it would normally be required there as a source of energy. The hyperglycæmia initiated by glucagon secretion is considered to stimulate the release of extra insulin which in turn accelerates the utilization of the transferred carbohydrate. Anderson[20] believes that he has found evidence for this kind of interaction of glucagon and insulin observable in the minute-to-minute fluctuations in the blood sugar levels of the dog and of man.

Opinion is divided on whether glucagon has any action in animals without insulin other than to mobilize liver glycogen.[21, 22] In human subjects with a normal endogenous insulin supply, glucagon-Lilly has been reported in one study to cause no inhibition and possibly to enhance,[23] and in another definitely to enhance,[24] the peripheral utilization of glucose.

Glucagon-Lilly has been used in an investigation of the mechanism of satiety in normal man.[25] Sensations of hunger and intensity of gastric contractions as well as capillary and venous plasma glucose levels were recorded simultaneously before, during and after the intravenous injection of glucagon-Lilly. In each of 16 such experiments, gastric contractions ceased within three minutes of the start of the glucagon injection, followed by disappearance of the hunger sensations and by a coincident increase in glucose utilization. This experiment has much to commend it, in that previous studies of the above phenomena have entailed the administration of glucose in hypertonic solutions or at an unphysiological point of entry into the blood stream. The possibility that injected glucose differs from that already present in the blood plasma is also avoided.

The possibility that extracted glucagon might prove useful in setting up an index of one aspect of liver function has been explored.[26] Following continuous intravenous injection of glucagon-Lilly by itself into 10 normal subjects and eight patients with parenchymal liver disease, the differentiation in the hyperglycæmic response of these two groups was unsatisfactory. When the same procedure was used but with a small subcutaneous injection of epinephrine included, a distinct difference in the hyperglycæmic responses of the same two groups of subjects was obtained.

Glucagon and Conditions Involving Hypoglycæmia

The intravenous administration of extracted glucagon has been shown to be effective in the rabbit in relieving hypoglycæmia caused by insulin.[12] It has been administered to several children with glycogen storage disease. Of four patients studied in this way, three showed no response. The fourth, an infant, was described as showing a prolonged and marked rise in blood sugar level after a small dose of extracted glucagon.[27] The intravenous injection of glucagon-Lilly in doses ranging from 3 to 12 μg./kg. of body weight in a boy, aged 7 years and 5 months, with glycogen storage disease, failed to raise the blood sugar level.[28] Several distinct

types of glycogen storage disease in man have been recognized biochemically,[29] so that a single pattern of response to extracted glucagon should not be expected.

Histories of spontaneous hypoglycæmia associated with the absence of pancreatic alpha cells in children from the same family[30] and in a gastrectomized man[31] are of interest in view of the hypothesis that the alpha cells represent a site of origin and storage of glucagon. There is, however, no indication that extracted glucagon was employed in exploratory tests on any of these subjects.

GLUCAGON AND DIABETES MELLITUS

The diabetogenic action of injected pituitary growth hormone in certain species is well established. It is, therefore, of basic interest that the parenteral administration of pituitary growth hormone increases the release of a hyperglycæmic factor into the portal vein, presumably from the pancreas, in rats, cats and dogs[3, 10, 32] and also in man.[33]

However, this does not appear to constitute the entire diabetogenic action of growth hormone in susceptible animals. A link between the prolonged administration of glucagon-Lilly and the incidence or aggravation of diabetes mellitus in rats and rabbits has been looked for but not found by several investigators.[34-36] The administration twice daily of an unspecified dose of extracted glucose to rats force-fed a maximal diet high in carbohydrate increased an already present glycosuria. When cortisone, adrenocorticotrophic hormone or purified pituitary growth hormone was added to this treatment, the glycosuria became even more pronounced but did not continue after cessation of treatment.[37] Diabetogenic activity of glucagon-Lilly in oil, injected subcutaneously in large doses into force-fed rats and into normal dogs, has been observed.[38]

Either extracted glucagon plus inactivated insulin[39] or glucagon-Lilly[40, 41] acts to elevate the blood sugar level in diabetic as well as non-diabetic human subjects. The elevation in blood sugar level was greater under circumstances where the amount of liver glycogen was presumed to be increased. Epinephrine and glucagon-Lilly administered simultaneously to man may not act in the same way on the glycogenolytic system of the liver, as there is enhancement and prolongation of the hyperglycæmic action of the one by the other.[23, 26]

The earlier evidence bearing on the possibility that glucagon might play a part in the incidence or maintenance of diabetes in man has been reviewed by Pincus and Rutman.[27] As they pointed out, there is now consistent evidence that diabetes arising in adult man is not commonly a result of a simple insulin deficiency,[42-44, 46, 47] but they conclude that, in the light of available evidence, glucagon is probably more important as a modifier of such diabetes than as its cause. Ferner[12] has marshalled histological and other evidence in support of the hypothesis that an increase of alpha cells relative to beta cells (and, by inference, an increase in the secretion of glucagon relative to insulin) is pathognomonic for all known forms of diabetes. The recent findings from Germany concerning the reduction of blood and urine sugar levels in some classes of maturity-onset diabetic human subjects by BZ-55 (N_1-sulfanilyl-N_2-n-butyl-carbamide) have been interpreted by their authors in terms of Ferner's hypothesis.[45-47]

Several marketed insulin preparations have been shown to contain measurable amounts of extracted glucagon.[48] The same is true of many crude insulin extracts. These conditions raise basic questions relative to the use of insulin in the treatment of diabetes mellitus. What effects, if any, does the presence of extracted glucagon in insulin solutions have on assays designed to determine the insulin concentrations? What effects does extracted glucagon in marketed insulin solutions have on the therapeutic activity of the insulin?

Effects of added glucagon-Lilly on the determination of insulin potency by rabbit and mouse-convulsion methods of assay have been studied with the finding that even large inclusions have no significant effect on the insulin assay results.[49] No pathological changes could be detected in rats and rabbits following the prolonged administration of large amounts of glucagon-Lilly either by subcutaneous or intravenous injection.[34] It therefore appears likely that insulin preparations containing extracted glucagon would be just as effective as pure insulin in the treatment of diabetes mellitus. This conclusion is not a completely unanimous one.[14]

RETROSPECT AND PROSPECT

While recognition of the existence of a hyperglycæmic-glycogenolytic factor of the pancreas

known as glucagon is widespread, and some of its properties and actions have been outlined, the latter remain uncertain in part because of difficulties in terminology. In other words, the simple question, "What is meant by glucagon?", still requires a conclusive answer. The availability, to research workers, of a highly purified extract (glucagon-Lilly) has helped in this regard. Answers to the subsequent questions, "Is glucagon a hormone?", "When will it be made available to the medical profession?", still await the discovery of a proven means for removing its site of origin from living subjects in the first instance, and of obtaining an extract the properties of which correspond with the secreted factor in the second.

Within these limitations several interesting techniques and lines of investigation, especially as they apply to carbohydrate metabolism and its disorders, have been opened up through studies of glucagon action and through studies with extracted glucagon preparations. One of the clearest indications from these studies is that the positive effects of glucagon and its extracts are most evident when their actions are considered in concert with recognized hormones. For example, physiologically effective doses of injected glucagon extracts have not proven to be diabetogenic, but may prove to be so, even in the presence of endogenous insulin, when associated with hyperactivity of the adrenal cortex. Much larger doses of extracted glucagon are diabetogenic, and may possibly elicit such adrenal hyperactivity.

It appears reasonable to anticipate that slow-acting glucagon preparations will be developed, and that these may prove to have therapeutic value with minimal side-effects in the treatment of hypoglycæmia associated with some pathological conditions. The possibilities that glucagon hypersecretion may be an etiological factor in many cases of maturity-onset diabetes in man and in mice with the hereditary obese-hyperglycæmic syndrome are currently under investigation.

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NYLON STOCKING DERMATITIS

Six cases of dermatitis from nylon stockings are reported by Calnan and Wilson (*Brit. M. J.*, 1: 147, 1956). The eruption is usually symmetrical and most frequently involves the dorsa of the feet and toes, the backs of the knees, and the inner part of the upper thighs. All six cases gave positive patch tests to azo type dye and negative patch tests to pure nylon. Apparently all nylon stockings made in England are dyed with the azo dyes. Nylon stockings dyed with anthraquinone type dyes caused no trouble. Two of the 6 patients also had a dermatitis from nylon hair nets.

THE EFFECTS OF GLUCAGON ON CARBOHYDRATE METABOLISM IN PATIENTS WITH DIABETES MELLITUS*

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IN 1923 KIMBALL AND MURLIN[1] reported the occurrence of transient hyperglycæmia following the administration of crude extracts of pancreas containing insulin. To describe the hyperglycæmic factor or factors they proposed the term "glucagon", later also called the hyperglycæmic-glycogenolytic factor (H.G.F.). This substance, which is postulated to be a product of the alpha cells of the islets of Langerhans, has been crystallized by Staub, Sinn and Behrens.[2] An excellent review of the investigations which have been performed to determine the role of glucagon in carbohydrate metabolism has recently been published by Pincus and Rutman.[3]

Studies in human subjects have not yielded uniform findings. Using a relatively impure preparation of glucagon, Pincus[4] found that it caused a moderate rise in blood sugar levels in normal persons and in patients with stable diabetes, and a more marked rise in those with labile diabetes. Normal subjects and those with a stable form of diabetes showed rises of blood sugar averaging 13.2 and 17.5 mg. per 100 c.c. respectively. The average rise for those with labile diabetes was 57.7 mg. per 100 c.c. Recently Kirtley *et al.*,[5] using highly purified glucagon, found that the stable diabetic had a greater and more prolonged rise in blood sugar than the unstable diabetic. They tested their patients in the fasting state, whereas Pincus's patients had taken their usual breakfast and insulin. Kirtley and his co-workers administered glucagon intravenously in doses of 20 units per kg. body weight, over a half-hour period. Typically, their stable diabetic patients showed about 60 mg. % rise in blood glucose levels and the unstable ones about 25 mg. %. The highest blood glucose rise occurred 30 minutes after the injection.

These studies did not make clear whether any relationship existed between the degree of control of the diabetic state and the response to glucagon. The following investigation was undertaken in an attempt to clarify this point and to extend knowledge of the response to glucagon in diabetic patients.

PROCEDURE

Seven white adult male patients with diabetes mellitus were studied. All had maturity-onset diabetes which was easily controlled. One was 24 years old and the others were between 68 and 76 years. Two were obese. All studies were performed with the patient in the fasting state, the last meal being taken at 8 p.m. on the night before the test. At 8 a.m., 6 to 8 ml. of venous blood was withdrawn from the antecubital vein, and an intravenous solution of normal saline started. This was continued until 8:30 a.m., during which time the flow was regulated. At 8:30 a.m. a solution containing 150 ml. of normal saline and 2 ml. of glucagon* was started and administered by constant infusion over the period of half an hour. Blood was withdrawn from the opposite antecubital vein at 8:30 a.m. and at 15-minute intervals until 9:30; at 10:00, 10:30 and 11:00, except in patients 1 and 2, in whom 10:00 a.m. and 11:00 a.m. samples were not studied. After the test, food was taken. When the test included the administration of insulin, it was given at 8:00 a.m. If not, and the test was performed during a period when insulin was taken daily, it was given on completion of the test.

In Cases 2, 3, 5, 6 and 7, studies were first performed when the diabetes mellitus was uncontrolled and again after control had been achieved. In Cases 1 and 4 the tests were performed during adequate diabetic control. Insulin was withheld for periods described below, and the response to glucagon was again determined. The dietary intake for each patient was constant throughout the period of study. All patients received only NPH insulin when insulin was given, except for patient number 1 who was also given regular insulin.

The following biochemical determinations were made: blood sugar, cephalin cholesterol flocculation, serum proteins, albumin and globulins, thymol turbidity, serum alkaline phosphatase, serum cholesterol, serum phospholipids,

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*Glucagon—The Lilly Research Laboratories, Eli Lilly and Company, Indianapolis 6, Ind., U.S.A. Lot No. 208-158B-214 was used in all tests for cases 1, 2 and 3, except for the test performed on May 24 in case 3, when Lot No. 208-158B-214A was given. This latter preparation was also given in cases 4 to 7.

TABLE I.

BLOOD SUGAR VALUES.

Test	Date	8.00 a.m.	8.30 a.m.	8.45 a.m.	9.00 a.m.	9.15 a.m.	9.30 a.m.	10.00 a.m.	10.30 a.m.	11.00 a.m.	3.00 p.m.
CASE 1—D.B.W.											
Saline —Insulin	Feb. 4	84	89	82	79	73	70	..	40	..	52
Saline —No Insulin	Feb. 7	83	85	86	94	97	97	..	109	..	90
Glucagon—Insulin	Feb. 9	127	130	162	185	204	210	..	168	..	91
Glucagon—No Insulin	Feb. 11	68	79	109	144	180	188	..	150	..	..
Glucagon—No Insulin	Mar. 1	254	254	278	290	320	344	..	294	..	302
Glucagon—No Insulin	Mar. 3	268	254	266	240	254	254	..	244	..	262
Glucagon—No Insulin	Mar. 10	278	266	286	316	328	338	..	296	..	330
CASE 2—C.W.H.											
Glucagon—No Insulin	Feb. 15	204	210	212	228	240	228	..	220	..	358
Glucagon—Insulin	Mar. 14	77	81	109	151	131	119	..	38	..	94
Glucagon—No Insulin	Mar. 16	113	116	155	184	209	225	..	183	..	113
Saline —No insulin	Mar. 18	98	104	92	90	89	95	..	98	..	108
CASE 3—P.N.C.											
Saline —No Insulin	Mar. 21	133	137	148	150	155	148	147	141	138	135
Glucagon—No Insulin	Mar. 23	139	139	175	201	209	215	196	182	168	122
Glucagon—No Insulin	Apr. 4	104	105	123	179	197	213	192	180	166	99
Glucagon—Insulin	Apr. 6	106	111	140	176	187	193	167	135	106	74
Saline —No Insulin	Apr. 13	111	111	111	107	107	105	109	110	110	119
Glucagon—No Insulin	May 24	90	95	133	188	207	211	181	171	144	69
Saline —Insulin	Oct. 25	99	97	92	83	78	75	65	48	37	77
CASE 4—W.J.H.											
Glucagon—Insulin	Apr. 15	73	75	97	134	151	155	113	94	77	195
Glucagon—No Insulin	Apr. 18	63	62	103	138	148	157	124	98	81	122
Saline —No Insulin	Apr. 20	65	74	70	68	67	63	67	69	74	180
Glucagon—No Insulin	Apr. 22	71	67	101	142	151	135	115	94	69	..
Glucagon—No Insulin	May 9	123	129	148	203	210	209	180	156	123	114
CASE 5—G.S.											
Saline —No Insulin	May 16	218	219	218	215	217	218	196	200	201	314
Glucagon—No Insulin	May 18	192	201	224	220	272	288	..	240	218	238
Glucagon—Insulin	May 24	147	136	175	198	218	221	194	149	121	196
Glucagon—No Insulin	May 25	155	156	190	209	235	250	240	206	190	176
Glucagon—Insulin	June 10	86	83	121	154	180	184	156	113	92	120
Glucagon—No Insulin	June 13	80	94	126	168	192	200	166	152	127	145
CASE 6—J.P.											
Saline —No Insulin	July 4	209	196	193	184	178	178	168	159	159	178
Glucagon—No Insulin	July 6	180	179	201	209	217	219	232	201	188	180
Glucagon—Insulin	Aug. 12	109	102	126	144	177	172	143	134	123	103
Glucagon—No Insulin	Aug. 16	79	79	94	147	165	176	155	135	124	109
Saline —No Insulin	Aug. 22	87	73	75	77	79	80	81	87	85	108
CASE 7—C.A.H.											
Saline —No Insulin	July 8	260	260	252	238	220	236	231	232	222	364
Glucagon—No Insulin	July 11	252	236	262	262	282	246	222	216	208	306
Glucagon—No Insulin	July 21	118	114	130	156	166	176	168	162	147	259
Glucagon—No Insulin	Aug. 2	77	75	99	137	139	145	144	126	120	207
Saline —No Insulin	Aug. 5	73	85	85	76	75	75	78	80	85	192
Glucagon—Insulin	Aug. 9	48	46	78	106	107	86	53	22	28	85

serum bilirubin, direct and indirect values; bromsulphalein retention, blood lactic acid, blood pyruvic acid, carbon-dioxide combining power,[6] prothrombin activity.[7]

RESULTS

Data regarding the seven patients are noted in Figs. 1-7; the results of the blood sugar determinations are shown in Table I and of the blood pyruvic and lactic acid determinations in Table II.

CASE 1. D.B.W., aged 73 (Fig. 1). Diabetes recognized in 1943. Daily insulin dosage laterally was 64 units of NPH and 20 units regular. Obese and diabetes poorly controlled.

Admitted December 9, 1954, with fractured humerus. Weight 192 lb. (68½ inches tall.) Liver not palpable. Received 75 to 84 units of NPH and 20 to 30 units of regular insulin daily. Diet—P. 70 g., F. 70 g., C. 150 g./day. Fasting blood sugar values varied from 114 to 312 mg. % with average of 197 mg. % (Folin-Wu—15 tests). On December 10 and 17, serum cholesterol was 205 and 175 mg. % respectively. On January 14, carbon-dioxide combining power, 71 vol. %; total serum bilirubin, 0.4 mg. %; cephalin cholesterol flocculation, 0; thymol turbidity, 10 units; bromsulphalein retention,

TABLE II.

BLOOD LACTIC AND PYRUVIC ACID VALUES.

Test	*Date*	*Lactic Acid 8.30 a.m.*	*Pyruvic Acid 8.30 a.m.*	*Lactic Acid 9.00 a.m.*	*Pyruvic Acid 9.00 a.m.*	*Lactic Acid 9.30 a.m.*	*Pyruvic Acid 9.30 a.m.*	*Lactic Acid 10.30 a.m.*	*Pyruvic Acid 10.30 a.m.*
CASE 1—D.B.W.									
Saline —Insulin	Feb. 4	7.0	.36	6.1	.32	4.9	.35	4.9	.39
Saline —No Insulin	Feb. 7	7.1	.35	6.6	.31	6.9	.37	7.2	.41
Glucagon—Insulin	Feb. 9	8.9	.35	8.8	.40	7.5	.40	7.5	.37
Glucagon—No Insulin	Feb. 11	6.9	.52	6.4	.54	5.8	.37	6.2	.40
Glucagon—No Insulin	Mar. 1	6.8	.40	6.6	.34	6.7	.37	5.7	.36
CASE 2—C.W.H.									
Glucagon—No Insulin	Feb. 15	10.2	.45	7.2	.42	8.3	.59	7.5	.32
Glucagon—Insulin	Mar. 14	8.4	.33	7.4	.33	8.4	..	8.3	.59
Glucagon—No Insulin	Mar. 16	24.8	.39	6.7	.40	5.1	.39	5.5	.56
Glucagon—No Insulin	Mar. 18	8.6	1.02	5.4	.75	5.2	.41	5.9	.32
CASE 3—P.N.C.									
Saline —No Insulin	Mar. 21	7.7	.36	6.3	.60	6.1	.46	6.4	.58
Glucagon—No Insulin	Mar. 23	8.7	.58	7.6	.76	6.3	.67	7.4	.54
Glucagon—No Insulin	Apr. 4	8.5	.43	5.5	.63	8.3	.58	6.4	.63
Glucagon—Insulin	Apr. 6	9.2	.64	7.2	.52	7.9	.66	7.7	.48
Saline —No Insulin	Apr. 13	7.6	.46	6.4	.63	6.1	.40	5.9	.49
CASE 4—W.J.H.									
Glucagon—Insulin	Apr. 15	7.1	.42	5.5	.46	5.2	.43	4.8	.53
Glucagon—No Insulin	Apr. 18	6.7	.43	6.1	.43	5.1	.51	8.6	.82
Saline —No Insulin	Apr. 20	14.1	.51	20.2	.79	4.9	.53	4.0	.64
Glucagon—No Insulin	May 9	6.1	.38	4.4	.46	5.6	.51	3.4	.46
CASE 5—G.S.									
Saline —No Insulin	May 16	7.0	..	7.9	..	7.1	..	6.4	..
Glucagon—No Insulin	May 18	7.3	..	7.4	..	5.3	..	9.1	..

5% (45 min.); prothrombin activity 100%. On January 17, serum albumin and globulins 4.8 and 2.6 g. % respectively. When he was transferred to the Clinical Investigation Unit on January 28, 1955, the insulin was increased to 90 units NPH and 30 units regular. Between January 28 and February 15, the average fasting blood sugar level was 109 mg. % (16 determinations) and the average 3 p.m. blood sugar level was 80 mg. % (12 determinations).

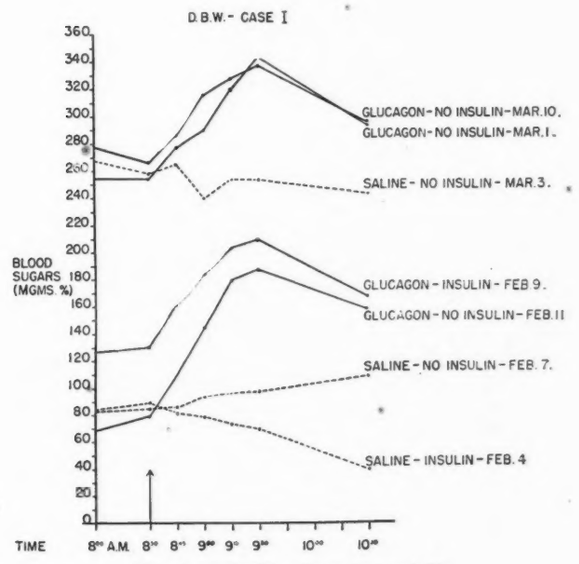

Fig. 1.—D.B.W.—Case 1, aged 73.

As noted in Figure 1, on February 4, a control test was performed using 150 ml. saline and 50 units of NPH insulin. Subsequent tests included: February 7, saline—no insulin; February 9, glucagon with 90 units NPH and 30 units regular insulin; February 11, glucagon—no insulin.

Insulin was reduced to 50 units on February 15 and to 30 units on February 18 and was discontinued on February 20. The blood sugar gradually rose until March 1, the average fasting level between February 15 and March 1 being 201 mg. % (14 determinations). Tests were performed as noted in Fig. 1. Between January 28 and March 10 he lost weight gradually from 184 to 168 lb. On March 3, serum cholesterol was 240 mg. %; phospholipids 8.0 mg. %.

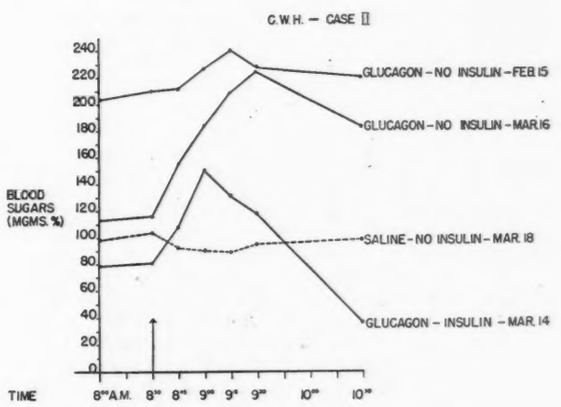

Fig. 2.—C.W.H.—Case 2, aged 24.

CASE 2. C.W.H., aged 24 (Fig. 2). Admitted February 14, 1955, with symptoms of diabetes mellitus for about four weeks. Blood sugar 286 mg. %, urine sugar plus 3, acetone strongly positive. Weight 162 lb., height 71½ inches. Liver not enlarged. He ate well.

The response to glucagon was determined on February 15, when the fasting blood sugar was 204 mg. % and the carbon-dioxide combining power 52 vols. %. NPH and regular insulin were started on completion of the test. After diabetes was controlled, the usual daily dose was 35 units NPH. The diet contained P. 125, F. 103 and C. 275 g.

On February 28, serum albumin and globulins were 4.7 and 2.6 g. %; thymol turbidity, 2.6 units; cephalin-cholesterol flocculation, negative; serum alkaline phosphatase, 6.0 King-Armstrong units; serum cholesterol, 235 mg. %. On March 8, serum phospholipids, 8.5 mg. %; total serum bilirubin, 0.5 mg. %, prothrombin activity, 88%; bromsulphalein retention, 1.7% (45 minutes).

Between February 25 and March 18, the average fasting blood sugar level was 104 mg. % (21 determinations); the average 3 p.m. blood sugar level was 81 mg. % (13 determinations). His weight rose to 167½ lb. Tests were performed as noted in Fig. 2. Insulin given on the morning of the test on March 14 was 35 units NPH.

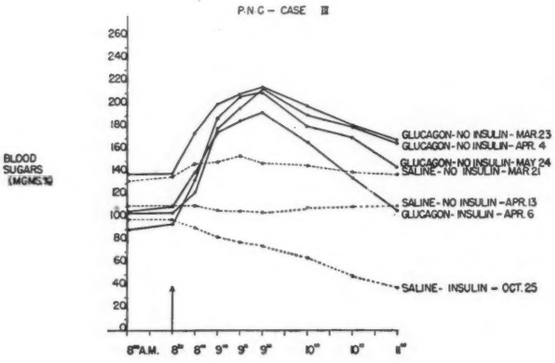

Fig. 3.—P.N.C.—Case 3, aged 72.

CASE 3. P.N.C., aged 72 (Fig. 3). Diagnosis of diabetes made March 1, 1955. Weight 130 lb., height 64½ inches. Liver not enlarged. Diet prescribed P. 74, F. 94, C. 196 g. Average fasting blood sugar level between March 12 and 20 was 144 mg. % (8 determinations); average 3 p.m. blood sugar level was 177 mg. % (5 determinations). On March 18, bromsulphalein retention was 4% (30 minutes), serum albumin and globulins, 5.2 and 2.1 g. respectively; total serum bilirubin, 0.5 mg. %; cephalin cholesterol flocculation, 0; thymol turbidity, 5.0 units. On March 22, serum alkaline phosphatase was 11.0 K.A. units; serum cholesterol, 310 mg. %.

On March 21, a control test was performed and two days later the response to glucagon was determined, after which insulin was first given. He received 15 units NPH for three days and 25 units a day thereafter until April 28 when the dose was increased to 30 units. Between March 24 and April 3 the average fasting blood sugar level was 117 mg. % (9 determinations); average 3 p.m. level 85 mg. % (7 determinations). On April 1, serum cholesterol was 275 mg. %.

On April 4 the response to glucagon was determined and two days later to glucagon with 30 units of NPH given on the morning of the test. After a period of good control, the response to glucagon without insulin on the morning of the test was again determined on May 24, 1955. Weight on May 24 was 126½ lb. A control test with 25 units of NPH insulin was made on October 25.

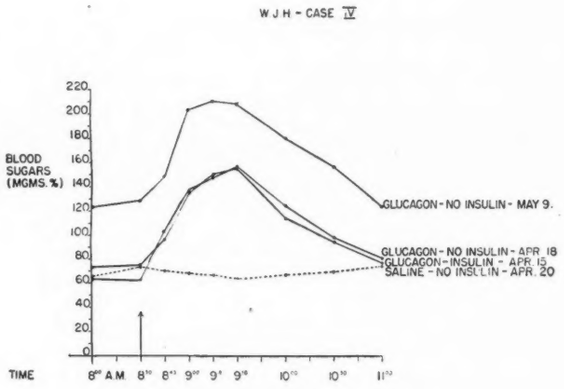

Fig. 4.—W.J.H.—Case 4, aged 72.

CASE 4. W.J.H., aged 72 (Fig. 4). Diabetes diagnosed in June 1948. Usual daily dose of insulin was 25 units PZ and 10 units regular insulin. In March 1955, 60 and later 75 units NPH insulin were prescribed. Between February 1954 and March 1955, fasting blood sugar levels varied from 192 to 332 mg. % (Folin-Wu).

Admitted March 24, 1955. Weight 164 lb., height 65 inches. Liver not enlarged. Diet prescribed—P. 68, F. 71, C. 155 g. On March 31, bromsulphalein retention 9.0% (30 minutes). April 1, serum albumin 5.4 g. %, serum globulins 3.1 g. %, serum cholesterol 355 mg. %, total serum bilirubin 0.6 mg. %, alkaline phosphatase 7.0 K.A. units, cephalin cholesterol flocculation 0, thymol turbidity 5.2 units, prothrombin activity 81%. In hospital he received 75 units NPH a day. Between March 26 and April 14, the average fasting blood sugar level was 102 mg. % (19 determinations); average 3 p.m. level, 119 mg. % (12 determinations). The response to glucagon with 75 units NPH given on the morning of the test was determined on April 15. Other tests performed are noted in Figure 4.

On April 22, insulin was discontinued. The average fasting blood sugar level until May 8 was 119 mg. % (17 determinations); average 3 p.m. level 159 mg. % (10 determinations). Weight gradually fell to 155 lb. on May 9, when the response to glucagon was determined. A myocardial infarction precluded further investigation.

CASE 5. G.S., aged 72 (Fig. 5). Admitted May 11, 1955, with symptoms of diabetes for about two months. Weighed 132¼ lb.; 65 inches tall. Liver not enlarged. Urinalysis: sugar plus 4; acetone, negative to trace. Fasting blood sugar levels on May 13, 14 and 15 were

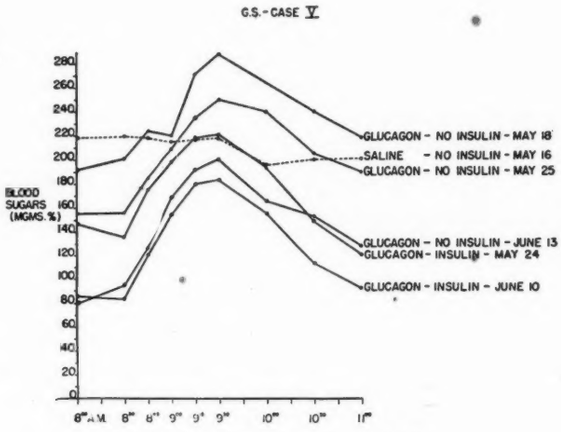

Fig. 5.—G.S.—Case 5, aged 72.

234, 212 and 226 mg. % respectively. On May 13, serum albumin 5.0 g. %, serum globulins 2.5 %, serum cholesterol 335 mg. %, serum phospholipids 12 mg. %, cephalin cholesterol flocculation plus 1, thymol turbidity 7.6 units, serum bilirubin 0.4 mg. %, alkaline phosphatase 6.0 K.A. units. Bromsulphalein retention was 6.5% (45 minutes).

On May 16 a control test with saline was made. Two days later the response to glucagon was determined, after which 20 units NPH insulin was given daily. The response to glucagon with 20 units NPH insulin on the morning of the test was determined on May 24, and without insulin on May 25, following which 30 units were given. The dose was increased to 40 units on May 29, and to 45 units daily on June 3. Between May 19 and June 2 the average fasting blood sugar level was 138 mg. % (15 determinations); average 3 p.m. level 178 mg. % (8 determinations). On May 26, cephalin cholesterol flocculation 0, thymol turbidity 5 units, serum cholesterol 240 mg. %, bromsulphalein retention 4.5% (45 min.).

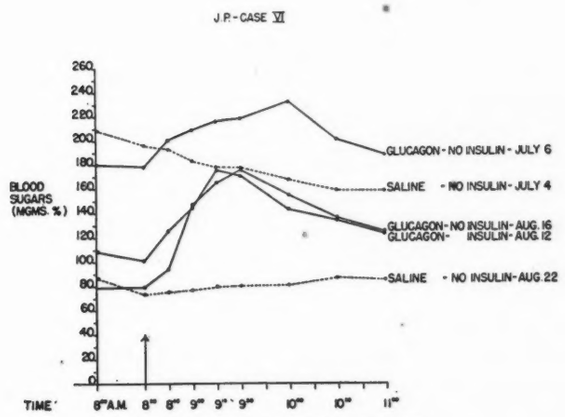

Fig. 6.—Case 6—J.P., aged 77.

Between June 3 and June 13 the average fasting blood sugar level was 86 mg. % (11 determinations); average 3 p.m. level 147 mg. % (5 determinations). His weight fluctuated between 132½ and 129½ lb. Tests were performed on June 10 and 13, as noted in Fig. 5.

CASE 6. J.P., aged 77 (Fig. 6). Diabetes mellitus recognized in 1950, after which he took 40 units PZ insulin daily irregularly. Diabetes poorly controlled.

Admitted June 30, 1955; weight 190½ lb., height 67 inches. Liver edge palpable about 2 cm. below costal margin in midclavicular line. From July 1 to 15 urine usually showed a trace of acetone. Average fasting blood sugar from July 1 to 14 was 176 mg. % (14 determinations; average 3 p.m. level 206 mg. % (9 determinations). July 5, total serum bilirubin 0.5 mg. %, serum albumin 5.0 g. %, globulins 2.0 g. %, serum cholesterol 305 mg. %, prothrombin activity 100%, cephalin cholesterol flocculation negative, thymol turbidity 6 units. July 7, bromsulphalein test 5.5% dye retention (30 min.). July 14, serum cholesterol 265 mg. %. Tests performed during the period of uncontrolled diabetes are noted in Fig. 6.

On July 15, he received 20 units NPH insulin daily, after which it was gradually increased to 65 units. Average fasting blood sugar from July 15 to July 31 and from August 1 to August 11 was 157 mg. % (17 determinations) and 174 mg. % (11 determinations) respectively; 3 p.m. levels for same periods were 111 mg. % (10 determinations) and 145 mg. % (8 determinations) respectively. On August 12 the response to glucagon with 65 units NPH insulin given on the morning of the test was determined. The average fasting blood sugar level on August 13, 14 and 15 was 83 mg. %. On August 16 the response to glucagon, without insulin on the morning of the test, was observed. Weight gradually decreased to 183 lb. by August 16.

CASE 7. C.A.H., aged 68 (Fig. 7). Admitted July 7, 1955, with symptoms for 18 months. Dehydrated. Urinalysis—sugar plus 4, acetone moderate. Nontender, sharp liver edge palpable 3 cm. below right costal margin in mid-clavicular line. Weight 129 lb., height 65½ inches. Fasting blood sugar July 8, 260 mg. %, carbon dioxide combining power 60 vols. %, serum albumin 4.6 g. %, serum globulins 1.8 g. %, serum cholesterol 370 mg. %, prothrombin activity 100%, serum bilirubin—direct 0.5 mg. %, total—1.3 mg. %, serum alkaline phosphatase 10 K.A. units, thymol turbidity 3 units. Bromsulphalein test—no dye detected. Fasting blood sugar levels on July 9 and 10 were 221 and 212 mg. %. Urinalysis showed trace to moderate acetone. Diet order P. 81, F. 84, C. 220 g. Control test with saline and no insulin was made on July 8.

Following the test with glucagon and no insulin on July 11, NPH insulin was given in a daily dose of 20

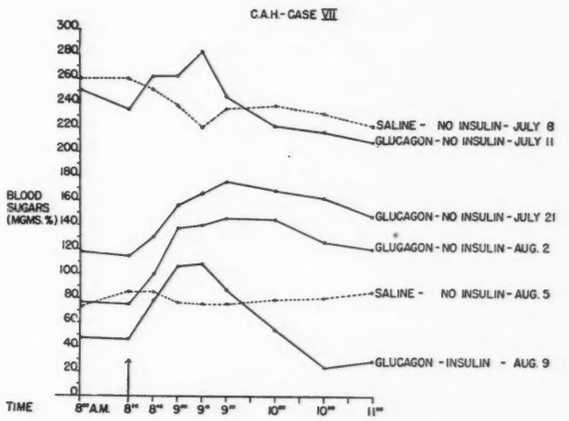

Fig. 7.—C.A.H.—Case 7, aged 68.

to 25 units. On July 12 serum bilirubin direct 0.4 mg. %, total 0.5 mg. %. Between July 12 and 20 the average fasting blood sugar level was 152 mg. % (9 determinations); 3 p.m. level was 199 mg. % (7 determinations). The response to glucagon, with no insulin on the morning of the test, was determined on July 21. Insulin was increased to 40 units, the dose subsequently used when insulin was given on the morning of a test. Between July 22 and August 2, the average fasting blood sugar level was 80 mg. % (11 determinations); average 3 p.m. level 149 mg. % (4 determinations). The study performed on July 21 was repeated on August 2. Between August 3 and August 9, during which time tests were performed as noted in Fig. 7, fasting blood sugar levels varied between 43 and 89 mg. %.

August 3, serum cholesterol, 210 mg. %. Results of the other liver function tests were similar to those above. August 9, bromsulphalein retention, 1.5% (30 min.). Liver size remained unchanged.

DISCUSSION

As can be seen from Table I, the intravenous administration of glucagon to patients with diabetes mellitus causes a rise in blood sugar levels as soon as 15 minutes after the injection. The maximum response usually occurs within one hour after the injection, whether insulin has been given or not. Following this, the blood sugar level falls. When insulin was omitted on the

morning of the test, the blood sugar level at the end of the test was still appreciably above the pre-injection level in five out of the seven cases. Even when insulin was given, the blood sugar at the end of the test was still above the pre-injection level in three cases. Although the hyperglycæmic response may persist longer than two and one-half hours, it is of interest to note that the response is usually transient and not sustained. The inability of glucagon to maintain sustained hyperglycæmia during more prolonged periods of administration has also been noted in other studies to be reported.[8]

The maximum rise in blood sugar levels when the patients were in good diabetic control varied from 70 to 109 mg. %, with values of 95 to 109 mg. % in six out of the seven patients (Table III).

TABLE III.

A COMPARISON OF THE MAXIMUM BLOOD SUGAR RESPONSE TO INTRAVENOUSLY ADMINISTERED GLUCAGON IN 7 PATIENTS STUDIED WHEN DIABETES MELLITUS WAS CONTROLLED AND UNCONTROLLED.

Case No.	*Diabetic state*	*Initial blood sugar mg. %*	*Highest blood sugar level following glucagon in mg. %*	*Rise in mg. %*	*Max. diff. mg. %*
1	Controlled	79	188	109	37
	Uncontrolled	266	338	72	
2	Controlled	116	225	109	79
	Uncontrolled	210	240	30	
3	Controlled	105	213	108	32
	Uncontrolled	139	215	76	
4	Controlled	62	157	95	14
	Uncontrolled	129	210	81	
5	Controlled	94	200	106	19
	Uncontrolled	201	288	87	
6	Controlled	79	176	97	43
	Uncontrolled	179	233	54	
7	Controlled	75	145	70	24
	Uncontrolled	236	282	46	

The magnitude of the hyperglycæmic response is considerably higher than that reported by Kirtley and co-workers,[5] and this may likely be attributed to the larger dose of glucagon employed in our studies. That the magnitude of response was similar when several tests were performed in the same patient, while in good diabetic control, is demonstrated in Case 3 (Fig. 3). When NPH insulin was administered on the morning of the test, the blood sugar levels did not rise to the extent observed when insulin was not given. A comparison of results of control studies (saline-insulin) with the glucagon-insulin tests in Cases 1 and 3 reveals that glucagon was able to prevent the hypoglycæmic effects of administered insulin. It was unable to do so, however, in Case 2.

Among the factors which determine the response to parenterally administered glucagon may be the state of diabetic control. From an analysis of our findings as recorded in Table III, it is apparent that the degree of hyperglycæmia after the intravenous administration of glucagon may differ when the diabetes is controlled and when it is not, the higher hyperglycæmic responses occurring when it is controlled. This was most apparent in Case 2, in which there was a maximum difference of 79 mg. %. Similarly, in Cases 6 and 1, the maximum response to glucagon was 43 mg. % and 37 mg. % higher respectively when tests were performed in the controlled as against the uncontrolled state.

In Case 7 there was a maximum difference of 24 mg. % between results of tests in the controlled and the uncontrolled state. A maximum difference of 32 mg. % occurred in Case 3. On May 24 a test was performed with another lot of glucagon.* The maximum blood sugar rise was only 8 mg. % greater than that noted previously.

In Case 4 there was a maximum difference of 14 mg. % between the response to glucagon in the controlled and uncontrolled states. However, the occurrence of a myocardial infarction prevented retesting after a longer period of poor control. Analysis of the tests performed in Case 5 reveals that the diabetic control bore no apparently significant relation to the maximum rise in blood sugar after glucagon administration.

Our findings, however, would suggest that in some patients the rise in blood sugar levels following intravenous injection of glucagon is less when the patient is in poor diabetic control than when the blood sugar levels are within the normal range. That the initial blood sugar level *per se* is not the limiting factor in the response to glucagon is suggested by Case 4, in which a rise from 266 to 338 mg. % was seen, and in Case 5 in which a rise from 201 to 288 mg. % occurred. The diabetes in all of the patients was of the maturity-onset type. All were in the older age group except the patient in Case 2, aged 24 years, who showed the largest difference in response to glucagon when studied in and out of diabetic control. In this small group of patients there was no correlation between the degree of response to glucagon and such factors as duration of diabetes, obesity, exogenous insulin requirements or laboratory evidence of hepatic dysfunction.

*Lot No. 208-158B-214A.

Kirtley and his co-workers have reported that the hyperglycæmic response to glucagon is greater in stable than in labile diabetics. They have considered that this difference depends upon the amount of available hepatic glycogen and that the unstable diabetic has less liver glycogen than the stable diabetic. If the response to glucagon does depend upon hepatic glycogen stores, it is considered likely that the state of diabetic control at the time of the test is a more important factor than whether the diabetes is stable or unstable. That there may be no correlation between amounts of histochemically demonstrable hepatic glycogen and such factors as previous state of diabetic control has been shown by Bogoch *et al.*[9] A lack of correlation between amounts of histochemically demonstrable hepatic glycogen and blood sugar concentrations has also been shown to exist.[9] It is likely therefore that there may be other factors that are responsible for differences observed in the hyperglycæmic response to glucagon. These may include the state of nutrition extant when glucagon is given, and the effect of available endogenous insulin. If available endogenous insulin is an important factor in determining the magnitude of the response to glucagon, further studies may enable this response to serve as a means of assessing available endogenous insulin.

Determinations of pyruvic acid after glucagon administration to four patients showed no significant changes (Table II). Lactic acid blood levels tended to fall, if anything, which suggests that muscle glycogen is not affected by glucagon.

SUMMARY AND CONCLUSIONS

1. The intravenous administration of glucagon to patients with controlled diabetes mellitus results in a significant rise in blood sugar levels.

2. Glucagon may protect against the hypoglycæmic effects of insulin in some patients with diabetes mellitus studied in the fasting state.

3. Our findings suggest that the state of diabetic control may determine the degree of the hyperglycæmic response to parenterally administered glucagon. In other patients no appreciable change occurred in the ranges of hyperglycæmic response when the patients were studied in and out of diabetic control.

4. No correlation was found between the response to glucagon and such factors as duration of diabetes, obesity, exogenous insulin requirements or biochemical evidence of hepatic dysfunction.

5. It is suggested that the hyperglycæmic response to the administration of glucagon may depend upon other factors than whether the diabetes is of stable or unstable type.

6. Determinations of blood lactic acid levels suggest that muscle glycogen plays no role in the hyperglycæmic response to glucagon.

We gratefully acknowledge the assistance of the nursing, dietary and laboratory staff of the Clinical Investigation Unit. The glucagon was kindly supplied by the Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Ind., U.S.A.

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RÉSUMÉ

Les auteurs ont cherché à mettre en évidence le relation qui existe entre le degré de contrôle du diabète chez un malade et sa réaction à l'administration de glucagone. Leurs recherches furent pratiquées sur 7 diabétiques adultes et facilement contrôlés. Il appert que le glucagone intraveineux cause une hyperglycémie chez les diabétiques dès quinze minutes après son injection et que cette action atteint son point culminant dans l'heure qui suit, et peut s'étendre au-delà de 2½ heures; elle se manifeste même en présence de l'administration d'insuline, mais à un moindre degré. L'analyse des résultats semblerait indiquer que la réaction hyperglycémique au glucagone est plus marquée chez les patients dont le diabète est le mieux contrôlé, et moins marquée si le malade est moins bien suivi. Le glucagone peut offrir une protection contre l'hypoglycémie chez le malade à jeun. Le taux de l'acide lactique du sang laisse supposer que le glycogène musculaire n'a aucune part dans l'action hyperglycémique du glucagone.

M.R.D.

COMPARISON OF RAPID INTRAVENOUSLY AND ORALLY ADMINISTERED CONTRAST MEDIUMS FOR ROUTINE GALLBLADDER STUDY

Gallbladder examination by both oral (Telepaque) and intravenous (Cholografin) methods was carried out by Kremens, Berger and Cohn (*New England J. Med.*, 254: 705, 1956) in 68 patients with biliary tract symptoms. While the intravenous method was more satisfactory diagnostically, the oral method should still remain routine because of its much greater simplicity and safety. Intravenous cholangiography should be used in the further investigation of all patients whose gallbladders are not visualized by oral Telepaque, as valuable additional diagnostic information can frequently be obtained.

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CONGENITAL MALFORMATION OF THE ANUS*

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CONGENITAL MALFORMATIONS of the anus are relatively uncommon and thus few surgeons have the opportunity to develop a significant personal experience in their management. It was thought that a review of those cases admitted to the Hospital for Sick Children, Toronto, and a discussion of their diagnosis, treatment, and final results would be worth while. One hundred cases of imperforate anus admitted from 1942 to 1951 inclusive form the basis of this report.

EMBRYOLOGY

It is helpful to think of this malformation as an arrest or variation in the fixed pattern of embryological development of the anus and rectum. The crucial period in the growth of this area is between the fifth and ninth weeks. At the fifth week there is a terminal cavity called the cloaca, which is common to both the urogenital and intestinal tracts, and separated from the exterior by the cloacal membrane. The lateral walls of the cloaca are ridged longitudinally on each side, demarcating the urogenital sinus anteriorly from the intestine posteriorly. In the sixth week a downgrowth of mesoderm occurs between the urogenital sinus and intestine, reducing the opening between the two septa to a small passage called the cloacal duct. By the seventh week the separation is complete and the cloacal duct is obliterated. The cloacal membrane has thus been divided into the urogenital membrane anteriorly and the anal membrane posteriorly. By the eighth week the urogenital sinus has acquired an opening through the urogenital membrane. However, the anal membrane is still closed. In the region of the future anus a dimpling of the ectodermal tissue develops, called the proctodæum. This continues to invaginate until approximately the ninth week, at which time the proctodæum and rectum establish continuity through the anal membrane.

If the urogenital groove is arrested in its downgrowth the urinary system will not be separated from the intestine, resulting in a persistent cloaca or a communicating fistula of varying size and position. The proctodæum may fail to invaginate to meet the descending rectum, thus resulting in a persistent anal membrane and imperforate anus. An incomplete rupture of this anal membrane results in a stenosis of the anal canal.

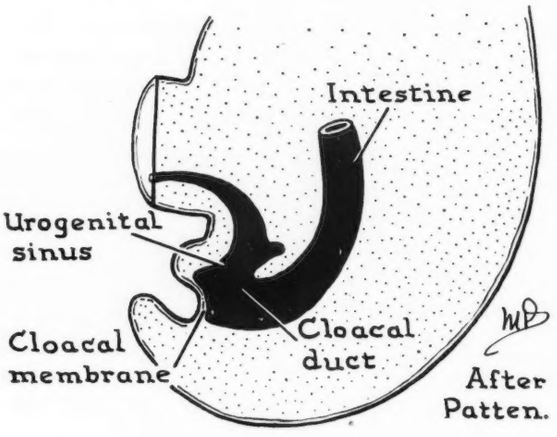

Fig. 1

The external anal sphincter is derived from regional mesenchyme, and is not involved in the above pattern. Therefore, the sphincter mechanism is usually found to be present despite the extent of other malformations.

CLASSIFICATION

Many classifications have been proposed. However, the simplified system of Ladd and Gross, presented in 1934, is the least complicated and most widely accepted. Each case, irrespective of associated fistulæ, can be placed in one of four groups:

Type I.—The anus and rectum are patent, but a stenosis of the anus or of the rectum is present.

Type II.—The anus is imperforate. The obstruction is membranous in character.

Type III.—The anus is imperforate. The rectal pouch ends blindly some distance above the anus.

Type IV.—The anus, the anal sphincter and the lower rectum are normal. However, the upper portion of the rectum ends blindly some distance from the lower pouch.

DISTRIBUTION OF CASES

These malformations occur more commonly in males than in females. In this series of 100 cases, 66 were in males. The distribution according to type and sex is shown in Table I.

*From the Department of Surgery, University of Toronto, and the Hospital for Sick Children, Toronto.

TABLE I.

	Type I	*Type II*	*Type III*	*Type IV*	*Total*
Male.....	8	8	49	1	66
Female.....	0	1	33	0	34
	8	9	82	1	100

FISTULÆ

Fistulæ of various types are so frequently associated with an imperforate anus that a careful examination for them should always be made preoperatively. These abnormal communications may lie between the rectum and the bladder, urethra, perineum or vagina. They are usually single but may be multiple. They are usually the result of faulty embryological development, but may be produced as a complication of surgical attempts to correct the original condition.

Investigation includes simple probing of the fistula, cystourethroscopy, and urography, and if possible, endoscopy and roentgenographic studies of the bowel.

TABLE II.

TYPES OF FISTULA

	Male	*Female*	*Total*
Recto-vaginal...	—	24	24
Recto-urethral..	8	0	8
Recto-perineal..	7	3	10
Recto-vesical...	6	1*	7
Totals.....	21	28	49

*Associated with a recto-vaginal fistula.

In this group there were 49 fistulæ, and of these the most common was a recto-vaginal fistula occurring in 24 of the 34 females. In most cases of the recto-vaginal type, the fistula was of sufficient diameter to permit spontaneous decompression of the rectum, and repair was deferred until the child was older. This is of considerable importance, in that there were no deaths in those babies with recto-vaginal fistula. On the other hand, the presence of an unrecognized or persistent recto-urethral or recto-vesical fistula, particularly in the male, was frequently the source of considerable morbidity and occasionally the cause of death due to associated pyelonephritis. The presence of this type of internal fistula may be suspected if pyuria and fever persist. Early repair is then mandatory, the aim of treatment being to obtain complete separation of the intestinal and urinary tracts with control of both outlets. The types of fistula and their distribution are shown in Table II.

ASSOCIATED ANOMALIES

This malformation is often associated with other anomalies, which are frequently multiple. They are usually of a serious nature and have much to do with the high mortality in this group of patients. Of the 100 cases, 37 had associated anomalies, the most frequent sites being the gastrointestinal, genitourinary and cardiovascular systems (Table III).

TABLE III.

FREQUENCY OF ASSOCIATED ABNORMALITIES

Tracheo-œsophageal fistula	7
Atresia of small intestine	2
Atresia of colon	1
Malrotation	3
Absence of gallbladder	2
Meckel's diverticulum	4
Polycystic kidneys	4
Horseshoe kidney	2
Urethral valve with hydroureter and hydronephrosis	2
Atresia of urethra	1
Double uterus	2
Septate vagina	1
Hypospadias	4
Undescended testes	3
Congenital heart disease	10
Mongolism	3
Myelomeningocele with hydrocephalus	4
Microcephaly	1
Skeletal defects	8
Hare lip	2

DIAGNOSIS

Most anal malformations can be readily detected by examination of the perineum at birth. The diagnosis of Type I abnormality may not be apparent for some time after birth, when obstipation or even obstruction develops. If the stenosis is marked, bulging of the perineum when the child strains at stool and the passage of ribbon-like stools are characteristic findings.

A Type II abnormality is easily diagnosed. Black meconium can be seen deep to the membrane. As the baby strains, a palpable impulse of meconium can be felt.

Type III abnormalities, the commonest group, present more variable findings. There is usually a dimpling in the region of the anus. If the skin of the area is stimulated, contraction of the external sphincter can be observed. The distance of the rectal pouch above the anal area usually cannot be estimated without special means.

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The difficulty encountered in the diagnosis of a Type IV abnormality, an uncommon anomaly, is exemplified by the one case in this series. The infant died on admission, two and a half days after birth. The anus appeared normal, but on digital examination of the rectum, a complete block could be felt about 1½ inches (4 cm.) above the anus. The findings were those of low intestinal obstruction, and death occurred on the day of admission from perforation of the cæcum and peritonitis.

TREATMENT

Type I.—The 8 cases were all treated by repeated dilatation of the stricture. This was done daily for 7-14 days, followed by less frequent dilatation for 3 to 6 months. Normal anal function was obtained in all cases, although there was one death in this group, due to an associated malrotation of the intestine complicated by a volvulus.

Type II.—The 9 cases were treated by excision, or by cruciate incision of the membrane followed by dilatation. There were no deaths in this group and a normal functioning anus resulted in all cases.

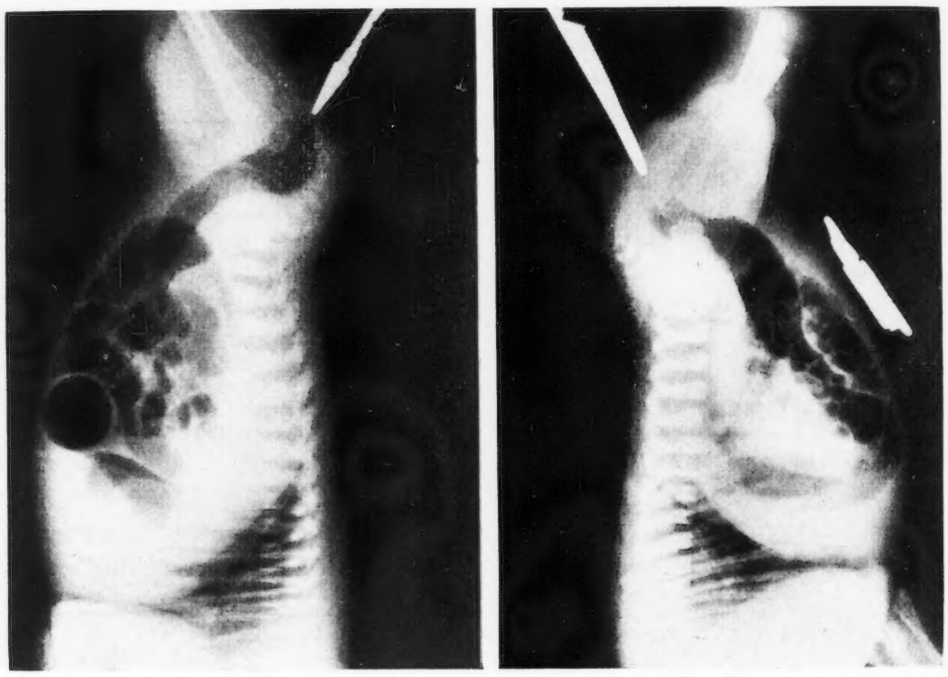

Fig. 2a

Fig. 2b

Fig. 2a.—Lateral film showing the blind rectal pouch close to the radio-opaque marker (treated by anoplasty). **Fig. 2b.**—A higher rectal pouch (treated by the abdomino-perineal operation).

Wangensteen and Rice in 1930 proposed the "inversion x-ray" method of determining the distance between the skin and the blind rectal pouch. The child is held in the inverted position with a radio-opaque marker over the anal dimple. The gas in the colon rises and outlines the extent of the pouch. Paine has demonstrated that the sigmoid colon and rectum filled with air in a series of normal newborn infants as early as six hours after birth. However, this method is considered more accurate when the baby is 18 to 24 hours old, or older. Occasionally gas may be visualized in the bladder, indicating the presence of a recto-vesical fistula. This method was used routinely in the present series, and lateral films were found to be most helpful (Fig. 2).

Type III.—Results of treatment in Type III were less satisfactory. The practice in this hospital has been to do a primary perineal operation (or anoplasty) if possible. Whether a case is amenable to treatment by this approach depends largely on the distance of the blind rectal pouch from the exterior. This can usually be estimated quite accurately by the "inversion x-ray" technique. If the pouch is within 1-2 cm. of the exterior, it can be easily freed and brought down to the perianal skin, care being taken to preserve the delicate external sphincter muscle.

If the pouch is higher, difficulty is encountered in adequately freeing the pouch, and tension of the suture lines results in a ring of fibrosis and eventual stenosis. The peritoneal cavity may also be entered, with resultant fæcal contamination.

In the higher pouches, or in the poor-risk infant, a transverse colon colostomy has been the usual procedure, followed in one to four years by a combined abdomino-perineal procedure.

However, for those babies having a high rectal pouch or an associated recto-urethral or recto-vesical fistula, the one-stage combined abdomino-perineal "pull through" type of operation, developed by Norris in 1949, is probably the procedure of choice. The abdomen is opened and the recto-sigmoid is dissected from the pelvic floor until the blind rectal pouch is isolated and mobile. Associated fistulæ are divided and their ends carefully oversewn. The rectum is then brought out through an incision in the centre of the sphincteric area, which can be readily recognized, and sutured to the peri-anal skin. This operation was done in three of the more recent cases.

TABLE IV.

TREATMENT OF TYPE III LESIONS

Type of Operation	*No. of cases*	*Satisfactory result*	*Died*
Anoplasty	39	20	19 (11)‡
Colostomy followed by an abdomino-perineal procedure at a later date	11	5*	6 (3)
Primary abdomino-perineal operation	3	2	1 (1)
Adequate fistula with closure at later date	19	18	1 (1)
No operation performed	10†		10

*Permanent colostomy necessary in two cases due to absence of rectum.
†Mongolism, death on admission, meningomyelocele with hydrocephalus.
‡Figures in parentheses are those cases in which death was considered to be due to associated anomalies.

The results of treatment in Type III lesions are shown in Table IV.

Of the 53 cases requiring immediate decompression, the perineal operation was done in 39 or 74%. The postoperative complications of this procedure, resulting in death, included inadequate freeing of the high rectal pouch in two cases with resultant gangrene of the terminal rectum and peritonitis; intestinal intoxication in three cases; and hydronephrosis and pyelonephritis associated with persistent recto-vesical fistula in four cases. These babies could have been treated more adequately by the abdomino-perineal operation. In this group as a whole there were 37 deaths, including those deaths which were considered due to associated anomalies and those in cases not subjected to surgical treatment for various reasons.

The results in those surviving operation are, in the main, fairly good. Except for two with a permanent colostomy and those awaiting the second-stage procedure, all have a functioning anus. All cases required dilatations postoperatively for a variable period. Some cases with a fibrotic ring in the area of the anastomosis required dilatation up to nine months postoperatively, and occasionally readmission for obstipation. However, even these cases eventually did well without revision.

Treatment required for the associated fistulæ varied with the size and type. The recto-urethral and recto-vesical fistulæ were closed at the time of the primary repair if possible. Occasionally a small recto-perineal fistula closed spontaneously after establishment of a functioning anus. Otherwise the fistulæ were excised six months to four years later. For babies with a large functioning recto-vaginal fistula, the usual treatment consisted of transfer and anastomosis of the fistulous tract to the centre of the sphincteric muscle to form a functioning anus. This was usually done in the second year of life and gave good results.

SUMMARY

A series of 100 cases of imperforate anus has been presented. These malformations were considered to be due to an arrest or aberration in the usual fixed pattern of development. According to the stage of arrest they were divided into four groups. The most common group, Type III, presented the greatest problem in management.

Approximately one-half of the cases were associated with fistulæ which, according to the size and site, were either an aid to treatment or a cause of concern.

Also frequently associated with the lesion were single or multiple congenital anomalies. These occurred so often and were of such importance clinically that their presence should always be suspected.

If the rectal pouch was close to the exterior, the perineal operation was found to give satisfactory results. Otherwise, for higher pouches or

those associated with recto-urethral or recto-vesical fistulæ, a primary abdomino-perineal operation, or a transverse colon colostomy as a first-stage procedure, is advised.

If an external fistula was found to be of adequate size for decompression, definitive operation was delayed for a period of months or years, with considerable decrease in mortality rate.

I wish to thank Dr. R. M. Wansbrough, Chief Surgeon, Hospital for Sick Children, for his advice in the preparation of this paper, and the Medical Art Department, Hospital for Sick Children, for the illustrations.

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RÉSUMÉ

L'auteur présente une série de cent cas d'anus imperforé. On considère que ces malformations sont causées par un arrêt ou une déviation du cours habituel du développement. On les divise en 4 groupes déterminés d'après la période où l'arrêt s'est produit. Le groupe le plus commun, le type III, est aussi le plus difficile à traiter.

Environ 50% des cas sont accompagnés de fistules, lesquelles, selon leur position et leurs dimensions, facilitent ou compliquent le traitement.

La lésion est souvent accompagnée aussi d'anomalies congénitales simples ou multiples. Elles se présentent si fréquemment et sont d'une telle importance au point de vue clinique qu'on doit toujours en soupçonner l'existence.

Lorsque l'ampoule rectale se trouve près de l'extérieur, l'opération périnéale donne des résultats satisfaisants. Autrement, dans les cas d'ampoules plus hautes ou d'ampoules accompagnées de fistule recto-urétrale ou recto-vésicale, on conseille l'opération abdomino-périnéale primaire ou la colostomie du côlon transverse comme premier stage du traitement.

S'il existe une fistule externe suffisante pour assurer la décompression, l'opération définitive peut être retardée pendant des mois, même des années, avec comme résultat un taux de mortalité considérablement diminué.

M.R.D.

LEUKÆMIC RETICULOENDOTHELIOSIS*

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THE PROBLEM of reticulosis and reticuloendotheliosis abounds in controversy. The questions as to the existence of leukæmic reticuloendotheliosis and as to its relation to other types of leukæmia have excited much interest among hæmatologists, not merely because of the rarity of the condition, but also because of the bearing its demonstration might have on the controversy over the status of the reticuloendothelial cell. These are merely a phase of the larger problem of the origin of blood cells in general and the relation of mature leukocytes to the more primitive cells of the reticuloendothelial system.

The term "leukæmic reticuloendotheliosis" was first coined by Ewald[1] in 1923. Later Fieschi,[2] on the basis of morphological studies, distinguished the following forms: (1) reticuloendotheliosis with primitive cells; (2) reticuloendotheliosis with monocytoid cells, this last variant corresponding to the "Schilling type" of American authors; (3) reticuloendotheliosis with lymphoid cells.

In reviewing the literature on the subject, it is apparent that little agreement exists among authors concerning the nature and the limits of leukæmic reticuloendotheliosis. The term unfortunately has been and still is used as a synonym for monocytic leukæmia, especially among American authors. Most workers feel, and we concur, that reticuloendothelial cells are precursors of lymphocytes, and under certain special conditions and stimuli, there may be hyperplasia of the reticuloendothelial cells with passage of both precursors and end-products into the peripheral blood.

This study of 49 cases of leukæmic reticuloendotheliosis was undertaken in the hope of better delineating the clinical entity and perhaps clarifying some of the confusion that has existed in the literature.

MATERIAL AND METHODS

Data on 49 cases seen at the Mayo Clinic from 1944 through 1953 have been studied. All satis-

*Abridgement of thesis submitted by Dr. Gosselin to the Faculty of the Graduate School of the University of Minnesota in partial fulfilment of the requirements for the degree of Master of Science in Medicine.

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factory smears of blood, bone marrow and splenic aspirates available to March 1954 were reviewed for cell types and indications of origin. Smears of bone marrow were available in the large majority of instances. In a few cases, fixed paraffin sections were also available and were reviewed. Differential counts of 500 nucleated cells on bone marrow smears, and of 200 white cells on peripheral blood, were recorded. Nucleated erythrocytes were noted per 100 leukocytes.

The members of the Hematology Laboratory of the Mayo Clinic aspirated the bone marrow and prepared the slides. The method of preparation of the aspirated marrow was similar to Schleicher's method, with slight modification.

CLINICAL ASPECT

The ubiquity of the reticuloendothelial cells makes leukæmic reticuloendotheliosis a very polymorphous clinical entity. Any organ of the body containing reticuloendothelial elements may be involved by the leukæmic process. However, in most cases the clinical manifestations result from disturbances or lesions in the spleen, liver, marrow and lymph nodes—those areas in which the reticuloendothelial system is most active. In rare cases, significant involvement may occur in the adventitia of vessels, in periglandular connective tissue, and so forth, giving rise therefore to a varied symptomatology.

The clinical picture will depend on the major sites of the hyperplasia, varying from primary, solitary involvement of one organ—for example, the spleen—to widespread infiltration of the entire reticuloendothelial system with systemic manifestations.

No specific or pathognomonic symptom, sign or clinical prototype exists. Each case has its own physiognomy. It must then be admitted that there are no clinical means to differentiate leukæmic reticuloendotheliosis from other malignant lesions of the reticulum, for example, lymphomas and leukæmias. Final differentiation is possible only by morphological evidence.

Leukæmic reticuloendotheliosis is a fatal disease with a course as irreversible as that of other leukæmias. The onset may be very insidious, and is often obscured by a history of some recent infection such as a common cold, influenza, otitis, tonsillitis, or gastrointestinal or even genitourinary infection. The presenting symptoms are quite variable: vague general symptoms like fatigability, "weakness", loss of weight, poor appetite, low-grade fever and, commonly, symptoms related to the anæmia (dyspnœa, palpitation, vertigo, and so forth). Evidence of a hæmorrhagic diathesis may often first be manifested by the occurrence of repeated attacks of epistaxis as well as by a generalized purpuric or petechial eruption. The main symptom may be an exfoliative dermatitis or another type of cutaneous involvement which we shall discuss later.

Physical examination may occasionally yield few striking changes. In most cases, however, the spleen, liver and skin are obviously involved.

TABLE I.

DEGREE OF CLINICAL INVOLVEMENT OF LIVER AND SPLEEN

Degree of involvement	*Liver*		*Spleen*	
	Cases	*%*	*Cases*	*%*
None	23	47	13	27
Slight	16	33	6	12
Moderate	9	18	13	27
Marked	1	2	17	34

Liver and spleen.—Splenomegaly is the most constant finding and the major clinical feature (73%) of our series. Degrees of enlargement are shown in Table I. This splenomegaly is usually progressive, although it may vary during remissions, spontaneous or therapeutic. In most cases it does not produce any secondary symptoms, except for a slight sensation of discomfort over the left upper quadrant of the abdomen. Occasionally, infarctions with varying degrees of perisplenitis will occur. In our cases there seemed to be no definite relationship between the degree of splenomegaly and the duration of the disease. Italian authors, however, have expressed the belief that the "pure splenic form" is the most frequent as well as the most benign.

Hepatomegaly is usually moderate. In only one of our cases was the inferior border of the liver below the umbilicus.

Lymph nodes.—Many authors claim that in 80 to 90% of cases there is marked involvement of the lymph nodes. Their patients presented themselves with enormous masses quite similar to those seen in Hodgkin's disease and involving both superficial and deep chains. The present survey is not in accord with these findings, as is shown in Table II.

In 10 of the 22 cases in which enlargement of lymph nodes was noted, there was marked in-

TABLE II.

DEGREE OF CLINICAL INVOLVEMENT OF LYMPH NODES

Degree of involvement	*Cases*	*%*
None	27	55
Slight	16	33
Moderate	6	12
Marked	0	0

volvement of the skin. We believe that the enlargement of these nodes was often due to a dermatopathic lymphadenitis (lipomelanotic reticulosis) as proved by biopsy in two cases. Lymph nodes were also biopsied in two other patients: one proved to be inflammatory while the other was reported as "malignant lymphoma."

TABLE III.

DEGREE OF CLINICAL INVOLVEMENT OF SKIN

Degree of involvement	*Cases*	*%*
None	35	72
Slight	2	4
Moderate	2	4
Marked	10	20

Skin (Table III).—Involvement of the skin is frequent in leukæmic reticuloendotheliosis, and many such cases have been reported. Cazal stated[3] that 20 to 25% of the patients present cutaneous manifestations. Bell[4] stated that "the skin is involved in about 10%. In the skin the infiltrations of leukæmic cells seem to begin around the dermal blood vessels, from which we may conclude that the undifferentiated mesenchyma is also involved in the leukæmic process."

Montgomery and Watkins[5] published data on four cases with exfoliative dermatitis as a manifestation of leukæmic reticuloendotheliosis. Case 1 belonged to the lymphocytic type, case 2 to the primitive cell type, cases 3 and 4 to the monocytic (Schilling's) type.

Epstein and MacEachern,[6] in an extensive study, have reviewed the dermatological manifestations of the lymphoblastoma-leukæmia group. Cazal[3] and de Graciansky and Paraf[7] have attempted to classify the cutaneous lesions found in leukæmic reticuloendotheliosis into two main groups: (1) non-specific cutaneous manifestations (pruritus, purpura, melanoderma, herpes zoster), and (2) so-called specific cutaneous lesions. The latter lesions have been said[3] to be a specific cellular infiltrate. "As one speaks of leukæmids in leukæmias, one could talk of reticulids in reticuloendotheliosis." Three types of lesions are most commonly encountered: (a) papular eruptions; (b) nodules, tumours, ulcerations; (c) erythroderma.[5]

From this series, one can conclude that no specific dermatological picture exists histologically or clinically and that lesions of the skin encountered in leukæmic reticuloendotheliosis are similar to those seen in any disease of the lymphoblastoma-leukæmia group.

HÆMATOLOGICAL ASPECT

The presence of an increased number of normal and abnormal reticular cells and reticular lymphocytes in the peripheral blood or in the bone-marrow aspirate should be considered as only one of the multiple localizations and manifestations of the disease.

Peripheral blood and reds cells (Fig. 1).—As a rule, marked anæmia is infrequent. When it occurs, it is a very serious prognostic sign. In this series, it was found only in the late stages of the disease. The anæmia is, in the majority of cases, normocytic and normochromic, although macrocytosis was found in 18 cases. This anæmia is progressive, and in none of the cases has its spontaneous or therapeutic reversion been noted during the course of the disease. No hæmolytic component was apparent in any of the cases. Rouleau formation of moderate degree was noted in 21 cases and the presence of normoblasts in five cases.

White cells (Fig. 1).—Leukopenia is a very important feature. It was observed in 28 cases (56%). The leukocyte count is usually around 2,000 to 3,000 per c.mm. of blood. It may reach critically low levels. In one case, agranulocytosis occurred and was rapidly followed by death. This situation, however, was most certainly secondary to administration of nitrogen mustard. Leukocytosis (more than 10,000) was present in 12 cases, the highest leukocyte count being 139,000. In 10 of these cases there were generalized cutaneous lesions with secondary infection. Differential counts have shown that neutropenia with distinct relative lymphocytosis is the rule. In rare cases, moderate eosinophilia (less than 10%) was encountered. The proportion of reticular cells and reticular lymphocytes was quite variable: from 1.5% to 89% with an average of 18%. One has, however, to bear in mind the relative accuracy of such counts because of the unavoidable listing of a certain pro-

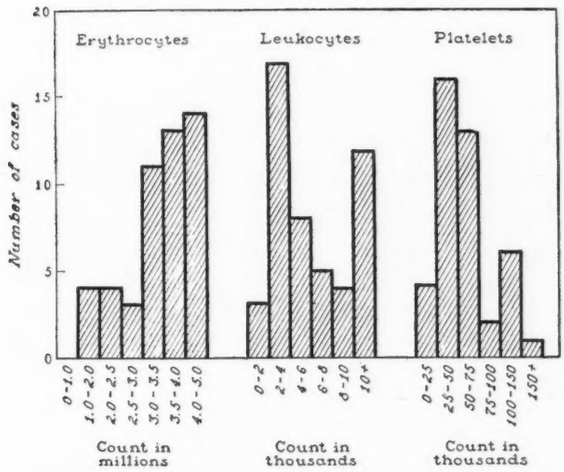

Fig. 1.—Frequency distributions of concentration of erythrocytes, leukocytes and platelets.

portion of reticular lymphocytes as mature lymphocytes.

Platelets (Fig. 1).—Thrombocytopenia (less than 100,000 platelets per c.mm. of blood) was observed in 35 of the 42 cases in which platelet counts were made. In only one case was the count above 150,000. Thrombocytopenia was manifest in the early stages and progressively increased during the course of the disease. Fourteen patients presented themselves with generalized petechiæ, and 28 had a history of bleeding (epistaxis, hæmoptysis, melæna, hæmatemesis, etc.).

Conclusions.—All in all, it may be stated that when the disease is in an advanced stage, one will find a pancytopenia or a reduction in the relative numbers of all formed elements of the peripheral blood, giving rise to the so-called myelophthisic type of picture due to extensive infiltration of marrow by reticular cells and reticular lymphocytes.

Bone marrow.—Smears or paraffin sections of bone marrow were available in 38 of our 49 patients. Those were carefully studied and differential counts of 500 cells were made.

Expressed as a percentage of the differential count, we considered the following as significant variations: red cell series, below 10%; myeloid series, below 35%; lymphocytes, above 10%; reticular cells, above 3%.

Our results were as follows: (1) erythropoiesis was depressed in 13 cases (34%); (2) myelopoiesis was depressed in 31 cases (82%); (3) lymphocytes were increased in 27 cases (71%); (4) reticular cells and reticular lymphocytes were increased in 37 cases (97%); (5) the myeloid-erythroid (M.E.) volume as determined by the hæmatocrit (normal = 4 to 8%) was less than 2% in 25 cases (66%); (6) the myeloid-erythroid ratio was around one or was reversed in 25 cases.

In six cases, only traces of normal myelopoiètic and erythropoietic cells were present. The bulk of the specific tissue was replaced by dense accumulations of large polymorphous reticuloendothelial cells.

In contrast to van der Meer and Zeldenrust[8] and in agreement with Moeschlin,[9] Leitner[10] and Rohr and Hegglin,[11] we believe that marrow aspiration may be of great help in the diagnosis of leukæmic reticuloendotheliosis. Sundberg,[12] discussing leukæmic reticuloendotheliosis in her monograph on sternal aspiration, stated: "The M.E. volumes obtained are extremely variable, but section preparations generally show evidence of hyperplasia. Smears show a marked increase in the reticular cells with evidence of transformation of these cells to leukocytes (granulocytes or lymphocytes). Blast forms which show morphologic evidence of their derivation from reticular cells are prominent. Erythropoiesis and platelet formation are generally atypical and depressed." Our findings in the present series of cases substantiate Dr. Sundberg's statement.

A diagnosis of leukæmic reticuloendotheliosis is more likely to be made, *in vivo*, in films of blood, marrow, lymph nodes or spleen in which the characteristic cells may be found. There is no doubt that this method is less misleading than that of fixation, with the consequent shrinkage of cells.

Most of the publications that have appeared on this subject have been on a pathological and anatomical basis without examination of the marrow or the spleen. It is almost impossible by the anatomical method to distinguish a myeloblastic leukæmia from a small cell sarcoma or a reticuloendotheliosis. The only way to distinguish them is by films in which one can study the proliferating reticuloendothelial cells and the degree of their differentiation.

These cells (undifferentiated reticular cells, hæmatopoietic reticular cells, reticular lymphocytes and their transitional stages to lymphocytes) have been extensively described by Sundberg and Downey[13] and by Sundberg.[14]

The atypical reticuloendothelial cells and reticular lymphocytes when found in blood

smears have "a superficial resemblance to monocytes; they are monocytoid and lymphocytoid but not true monocytes or lymphocytes" (Sundberg and Downey[13]).

The recognition of these cells in blood smears is not a difficult matter for the experienced hæmatologist, but they are frequently misinterpreted by many laboratory workers as monocytes or lymphocytes and the condition is often diagnosed as either "subacute monocytic leukæmia" or "subacute lymphocytic leukæmia."

Whenever the possibility of leukæmic reticuloendotheliosis needs to be considered, blood smears should be repeatedly examined for lymphocytoid forms.

In summary, it is impossible to make the diagnosis of leukæmic reticuloendotheliosis clinically on the basis of history, symptomatology or physical findings, since these are not specific and are quite similar to those encountered in the lympholeukæmia group of diseases. However, clinically, these patients may present (1) a history of preceding respiratory infection or so-called flu syndrome, which may appear as the initial manifestation; (2) systemic, nondescript symptoms such as fatigability, loss of weight, low-grade fever, and night sweats; (3) a short history of splenomegaly and occasionally hepatomegaly; (4) a mild and variable generalized lymphadenopathy; (5) cutaneous manifestations such as generalized erythroderma, mycosis fungoides, and other non-specific lesions of the skin.

The diagnosis rests on the finding in the blood and marrow smears of reticuloendothelial cells, reticular lymphocytes, and transitional stages to the mature lymphocytes, a mild to moderate, usually normocytic, but often macrocytic anæmia, leukopenia with relative lymphocytosis, thrombocytopenia, and hypoplasia of the bone marrow.

COURSE AND PROGNOSIS

Leukæmic reticuloendotheliosis is inexorably and universally fatal, death being usually due to a complicating hæmorrhage or an intercurrent infection. It is an irreversible disease against which the human body does not react and in which treatment is only palliative. From this standpoint, it behaves exactly like other diseases characterized by abnormal cellular division such as neoplasms and leukæmias. Reports of many cases have been published without the mention of a fatal course. In most of these instances, however, authors have described only one phase of the disease, believing that a permanent cure had taken place, while in fact the patient was only in prolonged remission. The follow-up had not been long enough to permit evolution of the true course of the disease.

The course is extremely variable and the disease may be manifested in three main forms—acute, subacute and chronic.

1. The acute type is rapidly progressive, with a clinical picture quite similar to that of acute leukæmias. Death may occur in a few weeks, or the course may be as long as six months. This form is rarely seen in cases of the lymphocytic type (5 to 8%), while it is much more frequent in the monocytic and primitive cell types. Four cases of the present series belong to the acute type.

2. The subacute type is more frequently encountered (35 to 40%), and usually consists of two successive phases. The first phase, which is the longer, is characterized by the clinical involvement of one or many organs, quite frequently the skin, and by low-grade systemic manifestations. This period is almost benign in appearance and the disease remains slowly progressive until the onset of the second phase, which is an acute exacerbation with the clinical picture seen in the acute type. Death follows rapidly.

3. The chronic type accounts for 45% of the cases in the present series. In many of these, the disease remained almost latent and extremely mild for prolonged periods of time, so that little disability resulted. With this type, the diagnosis may be established during a routine examination in which the patient is found to have splenomegaly or leukopenia. Typical blood and marrow pictures are then discovered. A few patients had noted mild symptoms for several years before consulting a physician. The course in this type is very chronic and is characterized by prolonged spontaneous or therapeutic remissions with remarkable subjective improvement which may last for months. These latent stages are followed by exacerbation of weakness and fatigability, and by relapses of variable intensity and duration. In four cases, the patient was known to have lived for more than 10 years after the onset of symptoms.

Radiotherapy remains, at the present time, the treatment of choice in these chronic cases, and

frequently the initial lesions vanish surprisingly well. However, progressive radioresistance develops and, from then on, nothing seems to influence the course of the disease.

One should be very careful in attempting to predict the definite course of an individual case on the basis of clinical or hæmatological findings. There exists no definite correlation between the clinical course and the morphological picture although (1) cases in which there is a higher proportion of primitive reticuloendothelial cells have a definite tendency to behave like acute leukæmias, and (2) there is a direct relationship between the activity of the bone marrow and the course of the disease, patients with hypoplastic marrow having a shorter survival time. The degree of activity of the bone marrow should also be considered before treatment is instituted, since most of the methods now used in the treatment of "leukæmias and allied conditions" are potent depressors of the bone marrow.

FOLLOW-UP

Of 49 patients studied in this series, 45 have been traced. By March 1954, 16 were still alive, 28 had died from leukæmic reticuloendotheliosis, and one had died from an unrelated cause (Tables IV, V, and VI).

TABLE IV.

STATUS OF PATIENTS AS OF MARCH 1954

Status of patient	*Patients*	*%*
Untraced	4	8
Living	16	33
Died from leukæmic reticuloendotheliosis	28	57
Died from unrelated cause	1	2
Total	49	100

TABLE V.

DURATION OF SYMPTOMS OF 28 PATIENTS WHO HAD DIED FROM LEUKÆMIC RETICULOENDOTHELIOSIS

Duration of symptoms (years)	*Patients*
1	4
2	9
3	7
4	3
5	1
6	0
7	1
8	0
9	1
10 or more	2
Average survival time	3.5 years

TABLE VI.

DURATION OF SYMPTOMS OF PATIENTS LIVING (MARCH 1954)

Duration of symptoms (years)	*Patients*
1	1
2	2
3	3
4	1
5	3
6	3
7	0
8	0
9	0
10 or more	3

CONCLUSIONS

1. Leukæmic reticuloendotheliosis is a definite and distinct hæmatological entity which may be of three main types: the primitive cell type, the monocytic type (Schilling's monocytic leukæmia), and the lymphocytic type.

2. The present study was mainly concerned with the lymphocytic type of leukæmic reticuloendotheliosis; 49 cases were studied from the clinical and hæmatological standpoints.

3. Although the clinical aspects of this disease do not greatly differ from those of leukæmias, the hæmatological picture is pathognomonic and is characterized by the presence, in the smears of blood and bone marrow, of undifferentiated reticular cells, hæmatopoietic reticular cells, reticular lymphocytes and transitional stages to the mature lymphocytes.

4. The prognosis, as in leukæmias, is inexorably fatal.

5. The course of the disease parallels that of leukæmias, and in the chronic type, patients may survive for 10 to 15 years.

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ANTIDOTES TO CURARIZING DRUGS*

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WHEN A CLINICIAN reviews the problem of the effectiveness of antidotes to curarizing drugs, he cannot fail to be impressed by the wide divergences in the results of pharmacological investigations of such agents. Even more striking is the schism which seems to exist between the laboratory and clinical administration of antidotes. Some of these differences are due to variations in method of study. Others are the result of divergences of basic outlook among anæsthetists. So much confusion has arisen, however, that it is necessary to reconsider the whole matter from the beginning.

METHODS OF PHARMACOLOGICAL STUDY

The problem about which the anæsthetist seeks the help of the pharmacologist is this. It is sometimes necessary in clinical work to reverse the action of a muscle-paralyzing agent, either because the technique of anæsthesia in use demands the maintenance of myoneural block until shortly before the end of the operation, or because an operation finishes unexpectedly early. For this purpose an antidote is required. Furthermore, the most immediate need is for some means of restoring the paralyzed muscles of breathing to normal. It therefore follows that the laboratory studies of antidotal activity most likely to be applicable to clinical work are those in which respiratory depression is manifestly reversed, or at least where curarization to a degree sufficient to produce serious respiratory depression is demonstrated before the administration of the antidote drug. For this reason evidence of antidotal activity based upon the rabbit head drop test, in which the animal's breathing continues more or less normally, is not necessarily of any great validity in clinical anæsthesia. The same holds for the mouse rotating cylinder test of Collier and his colleagues,[1] though both it and the rabbit head drop test are of great value in the assay of the potency of curarizing agents. By the same token, statements concerning antidotal activity which are based on experiments with a cat's muscle in a myograph are significant only if the record is calibrated. For if the muscle is loaded, as it often is, the lever movement may be abolished long before the occurrence of paralysis approximating in severity that produced in clinical anæsthesia.

Another variable in experimental studies is the anæsthetic given to the animal. As has been pointed out elsewhere,[2] the clinical conditions in which nitrous oxide and oxygen form the basis of anæsthesia are more closely mimicked when pentobarbital is given to the animal. On the other hand, the changes to be expected in a patient under cyclopropane, ether, or mixtures of the two are more likely to be reflected in experiments where animals have been given ether and chloralose.

Yet other difficulties in the interpretation of experimental studies of antidotes arise from species variation. For example, Tensilon will reverse the action of decamethonium in the dog[3] but not in the cat, except under very special circumstances. In this latter species d-tubocurarine will successfully undo paralysis produced by decamethonium[4] but in man the myoneural blocking effect of these two agents given in this order is additive.

There is yet another difficulty. Where light nitrous oxide and oxygen anæsthesia is being maintained for a fairly prolonged operation, relaxant drugs must be given repeatedly and often to the point of cumulation. On the other hand, in experimental studies there is a tendency to regard evidence of reversal of the action of a single dose of a curarizing drug as indicating significant antidotal activity. It may well be therefore that what is quite an adequate antidote in the laboratory may prove to be less reliable when it is used in clinical anæsthesia.

It is, however, necessary to have some pharmacological basis for the practice of clinical anæsthesia, and it is now necessary to review the various antidote drugs to consider how much of their pharmacological action is in fact transferable to the anæsthetized human subject.

The first point is that antidotes are on the whole most effective against typical depolarizing and typical competitive blockers. Substances whose action has some of the characteristics of both groups, the mixed blockers of Paton,[5] do not respond nearly so well. This is by no means unexpected; for there is a mutual antagonism between depolarizing and competitive myo-

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neural blocking activity. Substances which possess the characteristics of both groups must to some extent be, as it were, already their own antagonist[6] and thus are less likely to be reversed by ordinary antidote drugs.

ANTIDOTES TO DEPOLARIZING BLOCKERS

Depolarizing blockers may be reversed in two ways. First, pharmacologically inert substances may compete with them at the end-plate and displace them thence. As with all such competitions the competitor must have a chemical structure approximately the same as that of the myoneural blocker it displaces. In the case of decamethonium these requirements are fulfilled to some extent by penta- and hexamethonium.[7] In the case of di-thia-decamethonium,[8] which is also a myoneural blocker, antidotal activity is exerted by 3-thia-pentamethonium, 3-thia-hexamethonium, and 4-thia-heptamethonium. There is no drug of this type which exerts a comparable antagonistic effect to the well-known depolarizing blocker succinylcholine. This type of competition is completely specific so that 3-thia-pentamethonium does not antagonize decamethonium. Pentamethonium itself likewise has no antagonistic action to 5, 6-di-thia-decamethonium. Unfortunately the antidotes of this type, with the exception of 4-thia-heptamethonium,[9] have so marked an action on the autonomic nervous system as to make them useless clinically. Also the thia-substituted compounds are so alike in their action to the straight chain methoniums that they have not come to be used in clinical anæsthesia.

A few years ago in the laboratories of the Wellcome Research Institute, De Beer and his colleagues[10] found a substance, compound 49-204, which sufficiently approximated decamethonium in chemical structure to possess antidotal activity. It was, however, less specific in its action and would reverse 5, 6-di-thia-decamethonium also, although not succinylcholine. It had few side-actions in the experimental animal and seemed as if it would provide an effective antidote for clinical use in anæsthesia.[33] This substance had a myoneural blocking action of its own but this was of the type possessed by the d-tubocurarine. There is, as has already been indicated, an appreciable amount of antagonism between small doses of competitive myoneural blocking agents and the depolarizers. This perhaps explains why a substance which on superficial examination might seem unlikely to be able to compete particularly successfully with decamethonium, is in fact a fairly satisfactory antidote.

De Beer and his colleagues[11] extended their work on substances like 49-204 and eventually isolated a compound which would antagonize succinylcholine as well as decamethonium and its di-thia analogue, but unfortunately this last substance proved to have so much depressor activity that its use in man has not been so far thought justifiable.

From the point of view of the clinician, antidotes to depolarizing blocking agents are not often required, for it is possible to use the more rapidly acting members of this group in amounts which will permit of spontaneous recovery from curarization within relatively brief periods. On the whole, therefore, it is preferable with such drugs to assist respiration for the short time necessary for the recovery from the paralysis of breathing. It may be that in the odd case where decamethonium has been used, an antidote will be necessary when an operation finishes unexpectedly early, and for this purpose compound 49-204 can be given in doses of 50 mg.

This substance in fact has in man a mild effect on pulse and blood pressure similar to that of nicotinic acetylcholine, but this side-action is not so serious as to make it dangerous to use (Fig. 1).

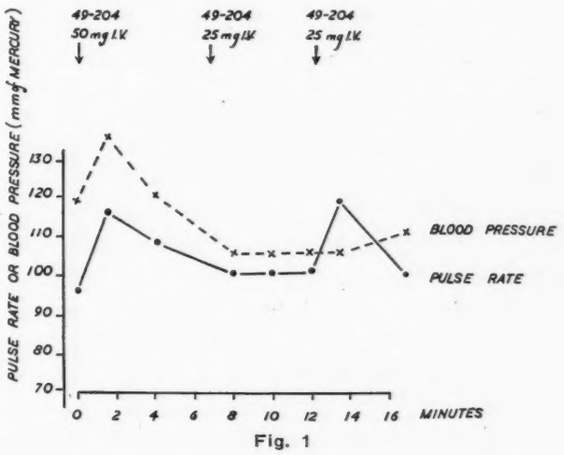

Fig. 1

It must be remembered, however, that the action of decamethonium if maintained for any considerable period in experimental animals spreads beyond the end-plate on to the adjacent part of the investing membrane of the muscle

fibre itself.[4] Depolarization which has extended so far is beyond the reach of antidotes, and neither 49-204 nor any other such drug can be expected fully to restore the response of muscle fibre to a nerve impulse once blocking of this type has developed. Such antagonist-resistant paralysis may arise also in man, and the author has noted it in a man who received 12.5 mg. of decamethonium in 35 minutes to control coughing during herniotomy. In this case it was possible to obtain only partial decurarization by the administration of 100 mg. of compound 49-204.

The problem of prolonged apnœa after the administration of succinylcholine has been discussed many times by other writers; suffice it to say that antagonists of the type described would almost certainly be useless in this type of case, for they represent instances of a degree of myoneural block far more profound than that normally studied in the laboratory.

ANTAGONISTS TO COMPETITIVE BLOCKERS

The so-called competitive blocking agents owe their specific action to an ability to reduce the proportion of the secreted acetylcholine which reaches the muscle end-plate. Antidotes to them must therefore either increase the total amount of acetylcholine penetrating to the end-plate or must increase the sensitivity of the end-plate to smaller amounts of acetylcholine. These two types of action will now be considered in more detail.

The drugs which characteristically increase the amount of acetylcholine reaching the end-plate in curarized subjects are the anticholinesterase substances, like physostigmine and the organic phosphates. The latter are relatively slow-acting drugs with actions on the central nervous system which completely preclude their use in clinical anæsthesia. Physostigmine, because it owes its activity to enzyme blocking, requires time to build up the necessary concentration of acetylcholine. It too is therefore not particularly suitable for use in clinical work, and even in the experimental animal is not a very effective reverser of profound curarization due to competitive agents.

The other type of antidote drug to competitive myoneural blocking agents is exemplified by Tensilon,[12-15] which is essentially an acetylcholine facilitator. It is true that it possesses a little anticholinesterase activity and there is some debate as to the importance of this in its antidotal action.[16-18] The extreme rapidity with which its action is manifest, however, compares very sharply with the slow recovery which is produced by the administration of physostigmine; also Tensilon has been shown by Randall[19] to reverse promptly ganglion block of the sympathetic, and the author[20] has found it equally effective in restoring function in the peripheral ganglia of the vagus. In addition, it immediately increases the normal response to acetylcholine in situations in the body where it is a physiological effector substance, e.g. at the vagal nerve endings and in the bowel.[21] It is, therefore, more satisfactory from the clinical point of view to forget the anticholinesterase activity of Tensilon and to regard it essentially as an acetylcholine facilitator. What electrophysiological evidence is available[22] certainly suggests that Tensilon owes its activity to its depolarizing properties at the end-plate, i.e. its action is partly to abolish the negative charge at the end-plate so that a smaller amount of acetylcholine is able to complete the process and initiate a contraction. It must be remembered, however, that Tensilon is a pharmacological stimulator and like all such drugs its action tends to be evanescent. The possibility of the return of curarization after its action has passed[23, 24] must therefore be always in the minds of those who use it to reverse the more profound types of myoneural block.

Neostigmine possesses in its chemical structure both the phenyl-tri-alkyl grouping of Tensilon and a urethane tail which gives its anticholinesterase activity.[25] It is, therefore, able to produce more or less immediate decurarization by acetylcholine facilitation, and to maintain the reversal of curarization by virtue of its anticholinesterase power. For this reason it is the agent of choice for the reversal of competitive myoneural blocking agents.

It must be remembered, however, that even neostigmine owes its antidotal power to an ability to upset the balance between the secreted acetylcholine and the blocker whose action is being reversed. It is conceivable, therefore, that where exceedingly large amounts of curarizing drug have been given over very long periods, cumulation at the end-plates may occur to the point at which neostigmine becomes relatively ineffective. Some such change may have been responsible in one of the author's cases for a

partial failure after the administration of this agent, which occurred in a patient who had been deeply curarized to obliterate a tendency to obstinate hiccup during cardio-œsophagectomy. He could be decurarized only to the point of the return of an adequate respiratory displacement but it was impossible to restore his myoneural function sufficiently to make him able to open his eyes and keep them open.

There are numerous possible explanations of neostigmine resistance appearing after relatively small doses of curarizing drugs. It may be due to latent myasthenia gravis which has been missed because a test dose has not been given.[26] It may be that the neostigmine itself sometimes becomes a myoneural blocking agent by virtue of its quaternary nitrogen group, or because the large amount of acetylcholine which it has produced permanently depolarizes endplates, with resulting loss of myoneural conduction. It is also possible that the disturbance is due to an upset of the potassium balance, although there is little direct evidence to support this conclusion save an accidental observation of Johnstone[27] that the intravenous injection of glucose and insulin will produce at least some recovery. It is also of significance that this type of failure to respond to neostigmine seems to develop almost exclusively in those with advanced peritonitis who almost certainly have a grossly distorted electrolyte balance.

ANTIDOTES IN CLINICAL ANÆSTHESIA

There are two possible methods of using relaxant drugs in anæsthesia. The anæsthetist may employ plane 1 nitrous oxide and oxygen narcosis, together with sufficient pethidine and barbiturate to guarantee analgesia and unconsciousness. Under such circumstances curarization will require to be maintained during abdominal operations until the peritoneum has been closed. In chest surgery, myoneural block of a fairly profound degree will be needed until controlled respiration is no longer necessary. Such an anæsthetist will find antidotes absolutely indispensable in his work, for he will be required not merely to restore an adequate respiratory exchange before the patient leaves the operating theatre; he will also find it necessary to decurarize all the muscles in his cases. Otherwise his rapidly awakening patient will complain bitterly of the subjective dyspnœa and choking sensation which are associated with residual curarization of the muscles of the throat.

On the other hand, particularly in surgical units where diathermy is not in regular use, the anæsthetist may prefer to use rather more profound general anæsthesia in his cases, perhaps with cyclopropane, ether, or mixtures of the two. He will then require relaxant drugs only to facilitate the more difficult stages of the operation. He will rarely find it necessary to employ curarization to aid abdominal closure and he will have comparatively little need for antidote drugs. Further, when he does employ them he will seek the reversal of relatively mild curarization in a patient who has received relatively small amounts of myoneural blocker. In such cases, where recovery of consciousness is almost certain to be delayed for an appreciable period, an antidote need only restore the breathing. Further, because the muscles of respiration have an enormous reserve, relatively incomplete restoration of their function will produce an adequate tidal exchange and therefore an apparently satisfactory response to the antagonist. In consequence, antidotes which are relatively safe, although not particularly efficient, will suffice. By contrast, the anæsthetist who seeks immediate and complete decurarization will have to use more potent agents which will, however, be less free from unwanted side-effects. It is important to realize that this divergence of outlook exists. Otherwise it cannot be appreciated that what is a satisfactory antidote to one anæsthetist may be quite useless to another.

THE SIDE-ACTIONS OF ANTIDOTE DRUGS

Finally there is the problem of the danger of using antidotes to competitive myoneural blocking agents. It has already been indicated that the most reliable drug is neostigmine but it is also well known that this is the only agent which has been reported as causing fatalities.[28-30] There seems little doubt that these tragedies were due to its muscarinic action. Some time ago the author followed the pulse rates of patients to whom neostigmine and atropine were given.[31] He was able to show that after the administration of these drugs there was always a progressive decline in the pulse rate, which reached a minimum some 5 to 10 minutes later, whether the atropine was given first or simultaneously with the antidote. Cardiac inhibition of some degree is therefore unavoidable after

the administration of neostigmine, and the only way to be certain that it does not progress to a dangerous extent is to follow the pulse rate with care during the danger period. Troublesome slowing of the heart is most to be expected in those whose pulses are already slow before the drug is given. Cardiac inhibition can be controlled by giving atropine, and if 1/100 grain is given with every 1.25 mg. of neostigmine no difficulty will arise in the majority of cases. In the exceptional instance where the pulse declines below 60 per minute the administration of an additional 1/100 grain of atropine will avert further danger. There is no need to fear an initial medullary vagal stimulation if doses of this size are injected rapidly into a vein.

The muscarinic activity of Tensilon[23, 24] is much less than that of neostigmine, and provided that 1/100 grain of atropine is given no serious trouble is likely even though as much as 20 mg. of the drug is given.

Just lately there has become available on the continent of Europe another anti-curare agent called Mestinon.[32] Its action in restoring breathing seems to be more permanent than that of Tensilon, though complete decurarization to the point of abolition of ptosis and paralysis of the throat muscles is not immediately attained after its administration. It has, however, the great advantage that effective doses of it seem to have considerably less muscarinic action than has neostigmine.

SUMMARY

The present confusion concerning antidotes to curarizing drugs can be resolved if it is realized that there is considerable species variation in the results of experimental studies of these agents. Also there are different techniques of the clinical administration of relaxant drugs.

Antidotes to depolarizing myoneural blockers act by competition and are therefore only relatively effective. Many of them have undesirable side-effects. Fortunately the agents of this group used in anæsthesia are so short-acting that antidotes are rarely necessary.

Antidotes to competitive blockers either increase the amount of acetylcholine reaching the end-plate or increase the responsiveness of the end-plate to the small amount of this substance which passes the barrier created by the blocker. Neostigmine possesses both these actions and is the most efficient antidote to this group of agents. Even it may fail in conditions of extreme myoneural block. It also may fail occasionally after quite ordinary doses of curarizing drugs, but it is not clear why this should happen.

Part of the confusion concerning the value of antidote drugs has arisen because some anæsthetists use them merely to restore normal breathing; relatively incomplete decurarization will do this. Other anæsthetists seek complete restoration of function even in the small muscles of the eyes and throat. Much more powerful antagonists are required for this purpose. Such agents tend to produce unwanted muscarinic actions which can be controlled by the administration of suitable doses of atropine.

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PHENYLKETONURIA:
A SURVEY OF CASES AT THE MANITOBA SCHOOL

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PHENYLKETONURIA, or phenylpyruvic oligophrenia, is a rare congenital metabolic disorder allied on the one hand with alkaptonuria and on the other with albinism. These are disorders in which the normal oxidation mechanism of phenylalanine and tyrosine metabolism is upset at various points. In alkaptonuria, homogentisic acid, a normal metabolite of tyrosine, is not oxidized further to acetoacetic acid but is excreted unchanged in the urine. In albinism, phenylalanine can be oxidized to tyrosine, but further conversion to melanin is blocked. The metabolic error in phenylketonuria occurs at a different point in the chain: phenylalanine cannot be converted to tyrosine; it accumulates, and its deamination product, phenylpyruvic acid, appears in the urine. The presence of this product is simple to test for, a few drops of 5% ferric chloride solution bringing out a bluish-green colour in previously acidulated urine.

Phenylpyruvic acid does not occur in the urine of normal people. In phenylketonurics, on the other hand, an average of one gram is excreted daily. Moreover, phenylalanine itself is excreted in abnormal amounts and other derivatives such as phenylacetoglutamine make their appearance. Failure to metabolize phenylalanine to tyrosine is more serious in its effects than the metabolic errors of alkaptonuria or albinism and is usually associated with a pronounced degree of mental defect.

There have been various estimates of the frequency of phenylketonuria. Jervis[5] estimated its incidence in the United States at 4 per 100,000, whilst in Britain Munro[10] formed a rather lower estimate of 2 per 100,000 of the general population. A recent Swedish estimate carried out by Larson[7] revealed that in that country the incidence was 2.5 per 100,000. Surveys amongst institutionalized mental defectives show similar variations. Jervis[5] from a survey of 20,300 institutionalized defectives in the United States established an incidence of 0.79% of phenylketonurics. From his institutionalized material in Britain, consisting of 2,457 cases, Munro[10] found a percentage of 1.22. Fölling, the original discoverer of the disease, carried out a survey with his co-workers in Norway[4] and established that 1.21% of 2,400 institutionalized defectives were phenylketonurics. Larson[7] found an incidence of 0.59% amongst 4,825 defectives. Jervis[5] analyzed the figures of 21 surveys carried out in different countries. Out of a total of 48,536 institutionalized defectives 312 phenylketonurics came to light, giving an estimate of 0.64% as the incidence of the disease in the defective population.

The degree of associated mental defect is generally severe, the bulk of cases being idiots or low-grade imbeciles. Levy and Perry[8] found that 82% were idiots amongst the 1,408 intellectually retarded children and 1,850 psychiatric patients whom they examined. Of the 29 cases described by Mautner and Quinn[9] none was above imbecile level. The 28 cases observed by Larson[7] included two of moron grade, and in the same paper this author recorded the occurrence of phenylketonuria in an intellectually subnormal man who was nevertheless able to support a family. Of Cowie's 15 cases[2] 14 were idiot or imbecile but the remaining member of the series was found to be of low average intelligence. On the whole, low-grade mental defect is the rule in this disease.

The genetic basis is a regressive gene with a heterozygote frequency of 1:100. It has been suggested that the normal allelomorph of the gene for phenylketonuria corresponds to the enzyme whose absence in this condition gives rise to the metabolic error. In the family history of such cases Tredgold[12] has stressed the pronounced psychopathic tendency in the form of psychosis, mental defect or epilepsy.

Reports of positive pathological findings are scanty. Alvord *et al.*[1] described the nervous system in five fatal cases. Two of these showed demyelination affecting the optic chiasma, the cortico-ponto-cerebellar and the cortico-spinal tracts; in a third case there was demyelination of the optic chiasma alone; and the two remaining cases showed no more than glial proliferation and increased fat about the blood vessels. Sander[11] in his case found hemiatrophy of the left hemisphere, with vascular changes and diffusely scattered perivascular areas presenting a flaky structure, mainly in the left extrapyramidal centres.

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The clinical picture is one of mental retardation, generally severe, associated with the excretion of phenylpyruvic acid in the urine, and accompanied by additional features. Pigmentary, osseous and neurological abnormalities have all been described as fairly constant accompaniments. Dilution of pigment is apparent in the skin, hair and iris. The skin is fair, smooth and fine in texture, and may exhibit photosensitivity, pigmented patches or eczema. The unusual fairness, or indeed pallor, is perhaps more apparent against a family background of darker complexion. The hair is blond or even colourless as in the albino, but darker colouring may occur. The iris is typically pale blue in colour. The skull tends to be slightly microcephalic, the maxilla may show mild expansion or prognathism with wide spacing of the incisors, and stature is sometimes reduced. Neurological anomalies have been noted in the sphere of deep reflexes, muscle tone and movements. The most constant finding is a generalized increase in deep reflexes, and this may be associated with increased excitability of the patient. Muscle tone is slightly increased but in some cases the increase may be so marked as to amount to rigidity. The stance is one of slight flexion at the hips and knees, ape-like or pithecoid, whilst the gait is awkward and tends to be stiff, short-stepped and on a broad base. Abnormal movements include body-rocking, similar to that of other low-grade defectives, coarse tremor of the hands, and, most characteristically, stereotyped or hyperkinetic movements of the fingers quite distinct from choreoathetosis. Epilepsy has been described in a number of cases, and on the E.E.G. an alternation of rapid and slow waves has been noted.

PRESENT SURVEY

The present survey is based on the institutionalized population of the Manitoba School. This, the mental deficiency centre for the province, houses a total of 793 defectives. A routine examination of the urine for phenylpyruvic acid disclosed seven cases with the characteristic reaction. A short description of these cases follows.

Charles M., aged 23.

The patient's mother was herself defective and died at his birth. The only sibling, a brother by a different father, is also a certified defective but is not a phenylketonuric. Information on earlier development is scanty but the patient was apparently tried at school, without benefit resulting, when 12 years of age. A year later he was admitted to the Manitoba School. Since then he has developed into a quiet, well-behaved defective, capable of simple routine ward work under supervision. He is easily excited and frightened, and the nursing staff have observed that on such occasions he becomes acutely tremulous, his legs give way and he sinks to his knees. These episodes are of brief duration and not associated with absences or loss of consciousness. Mental level is low-grade imbecility.

The urine contains 0.82 mg. of phenylpyruvic acid per c.c. and 0.239 mg. phenylalanine per c.c.

Complexion is pallid and skin is smooth in texture, with photosensitivity, pronounced dermographism and a few brownish patches. Hair is light-coloured and eyes are very pale blue. Skull circumference is 21½ inches and stature 5′ 6½″. Radiological report draws attention to large antra and frontal sinuses, and to diminished antero-posterior skull diameter with closed sutures. Neurological findings are generalized hyperreflexia with increased excitability, slightly increased muscle tone, an awkward broad-based stiff gait, and a fine tremor of the left hand. Stance is erect and there is neither body-rocking nor kinetic movements of the fingers. An alternation of rapid and slow waves has been noted on his E.E.G.

Hugo M., aged 26.

One of seven children; the others appear normal with the exception of a sister described as having subnormal intelligence. The patient's mother has been hospitalized for manic-depressive psychosis and a maternal aunt has been diagnosed as schizophrenic. The patient himself has been in an institution since the age of nine years. He walks with difficulty, has never learned to talk, is incontinent and requires every nursing care. His mental level is one of idiocy.

The urine contains 0.23 mg. phenylpyruvic acid per c.c. and 0.293 mg. phenylalanine per c.c.

Complexion is pale, dermographism is present, and the skin over his trunk shows a number of pigmented patches. Hair is fine and fair, and eyes are blue. Skull circumference is 21½″, pronounced maxillary prognathism occurs and stature is only 4′ 10″. Radiological report reveals widened maxillæ, large antra and frontal sinuses. Neurologically he shows generalized hyperreflexia. Muscle tone is increased to such an extent that walking is an effort. Stance is pithecoid and gait stiff and short-stepped on a broad basis. Body-rocking and hyperkinetic movements of the fingers are present.

Donald C., aged 27.

There are five children in this family, of whom two are normal and the remainder phenylketonurics. For five years between the ages of 42 and 47 the father suffered from a condition diagnosed as epilepsy. The patient has been in an institution since the age of 14 years. He is able to walk but cannot talk. He is incontinent and destructive. At the age of nine years he had an attack of poliomyelitis which left him with partial atrophy of the right calf and slight contracture of the tendo achillis. Mental level is that of idiocy.

The urine contains 0.60 mg. phenylpyruvic acid per c.c. and 0.206 mg. phenylalanine per c.c.

Skin is pale, smooth and photosensitive with dermographism. Hair is fine and fair and eyes are blue. Skull circumference is 21½″ and stature 5′ 7″. The radiologist has reported widening of the maxillæ with large antra, large frontal sinuses and apparent early closure of sutures. Reflexes are overactive and the patient shows a grossly exaggerated response to stimuli: any unusual noise or procedure causes him to double up. He has been described as exhibiting a state of constant apprehension. Muscle tone is increased, stance is pithecoid and gait stiff and short-stepped on a broad base. He shows both body-rocking and hyperkinetic movements of the fingers.

Terry C., aged 19.

The brother of the above, he has been in an institution since the age of 15 years. He is equally incontinent

and destructive, with the same mental grade of idiocy.

The urine contains 0.10 mg. phenylpyruvic acid per c.c. and 0.187 mg. phenylalanine per c.c.

Skin is pallid, smooth and photosensitive. Hair is fine and fair. Eyes, however, are brown. Skull circumference is 21¾" and stature 5' 6½". Widening of the maxillæ is visible on radiographs and the radiologist records that the cranial sutures appear to have closed early. The neurological picture is identical with that of the brother.

Shirley C., aged 14.

This girl, the sister of Donald and Terry, has been an inmate of the Manitoba School for 18 months. She is able to feed herself, dress and undress with help, and can talk, although with an extremely limited vocabulary. She has been described as nervous and distractable. Mental level is low-grade imbecility.

The urine contains 1.45 mg. phenylpyruvic acid per c.c. and 0.284 mg. phenylalanine per c.c.

Skin is pale and smooth, hair very fair and eyes blue. Skull circumference is 21½", maxillæ prominent, and stature 5' 3¼". Radiological examination shows wide maxillæ, large antra and frontal sinuses, with closure of sutures. Neurologically she demonstrates hyperreflexia, stiff, awkward gait, body-rocking and hyperkinetic movements of the fingers.

Cora W., aged 42.

She is one of three siblings, the others being normal. A cousin of the paternal grandmother was mentally defective. The patient has been an inmate of the school for 15 years. She is able to feed herself and can say a few words. She is reported as being unduly apprehensive and very easily upset. Mental level is low-grade imbecility.

The urine contains 0.95 mg. phenylpyruvic acid per c.c. and 0.282 mg. phenylalanine per c.c.

Skin is fair and smooth, hair fine and fair, and eyes blue. Skull circumference is 22", and stature 5' 5". X-ray examination shows wide maxillæ. Neurological findings are hyperreflexia, pithecoid stance, stiff, short-stepped broad-based gait, body-rocking and hyperkinetic movements of the fingers.

May M., aged 30.

A sister of this patient is epileptic and the father died of a cerebral neoplasm at the age of 41. The patient herself is the youngest of seven children and was born when the mother was 42 years of age. She did not walk until the age of 4 years or talk until she was 11 years old. Later she attended special classes in school for two years but was never able to read or write. When 14 years of age she was admitted to the Manitoba School. A quiet, co-operative defective, she is usefully employed as a laundry worker. Her mental grade is imbecility.

Urinary findings on this case have varied. At times the reaction to the ferric chloride test has been strongly positive, whilst at other times it has been negative. The specimen submitted for quantitative determination was collected when the patient was approaching a negative phase, and showed only 0.02 mg. phenylpyruvic acid per c.c. and mere traces of phenylalanine.

The patient is a fairly typical mongol defective, with a diminished stature of 4' 10", globoid skull, iris hypoplasia, fissured lips, roughened tongue and brachyphalangy. Radiologically she shows the small antra and underdeveloped frontal sinuses of mongolism. Skull circumference is 20½". Complexion is rather pale, eyes blue and hair brown. There are no unusual neurological findings. Clinically there appears little to distinguish her from other mongols.

DISCUSSION

From a routine examination for phenylketonuria carried out on the 793 inmates of the Manitoba School, seven cases of this metabolic abnormality were discovered. The first two cases, including rather surprisingly a typical example of mongoloid deficiency, had been diagnosed on the basis of the ferric chloride test. The next three were members of one family and presented a distinctive clinical picture quite apart from urinary findings, and this also applied to the remaining cases.

The percentage incidence of phenylketonuria in the institutional population worked out at 0.88. Mental level was low, with four imbeciles and three idiots.

The family histories would appear to lend support to the high incidence of psychic abnormality mentioned by Tredgold. The mother and only brother of one patient were mentally defective; the mother and maternal aunt of a second were psychotic whilst a sister was of subnormal intelligence; the father of the three phenylketonuric siblings had suffered for five years from a condition diagnosed as epilepsy. Of the remaining two patients the father of one died from a cerebral neoplasm while a sister was epileptic, and in the other a cousin of the paternal grandmother was mentally defective.

In the quantitative determination of phenylpyruvic acid and phenylalanine typical values were obtained except in one case. The amounts of these substances were estimated and compared with creatinine as a reference value, since the quantity of this latter substance is quite constant in 24 hours irrespective of diet. The results are as follows:

	Creatinine mg. per c.c.	*Phenylpyruvic Acid* mg. per c.c.	mg. per mg. Creatinine	*Alanine* mg. per c.c.	mg. per mg. Creatinine
Charles M.....	0.57	0.82	1.44	0.239	0.419
Hugo M.....	0.38	0.23	0.61	0.293	0.771
Donald C.....	0.45	0.60	1.33	0.206	0.457
Terry C.....	0.40	0.10	0.25	0.187	0.470
Shirley C.....	0.70	1.45	2.07	0.284	0.405
Cora W.....	0.58	0.95	1.64	0.282	0.486
May M.....	1.98	0.02	....	traces	....

Pigmentary changes were obvious in all cases except the mongol. The complexion was blond or pallid, the hair fine and light-coloured, and the eyes were with one exception blue.

Slight osseous changes were common. With the exception of the mongol all showed some bony abnormalities described in connection with phenylketonuria. The skull was slightly reduced in circumference in five cases. In four cases the radiologist reported early closure of sutures, in-

dicating a possible cause of the mild reduction in the size of the skull. In five cases radiography confirmed widening of the maxillæ. A further peculiarity was the large size of the maxillary antra and frontal sinuses. Stature, however, was markedly reduced in only one case.

Again excepting the mongol, all cases showed neurological features. The most constant finding was hyperreflexia, present in six instances. Muscle tone tended to be slightly increased, and in one patient this amounted to actual rigidity. Gait was stiff and awkward in six cases. Body-rocking and hyperkinetic movements of the fingers occurred in five cases while the sixth showed a fine tremor of the left hand. An increased excitability was noted in five patients.

The mongol whose urine gave a positive reaction for phenylketonuria showed none of the pigmentary, osseous or neurological accompaniments of this disorder. In view of the phasic nature of excretion, the biochemical error would appear to be incomplete or compensated, as suggested in Cowie's case.[2] Further investigation is being undertaken with a view to determining the exact nature of the abnormal metabolites.

SUMMARY

In a survey of phenylketonurics carried out at the Manitoba School seven cases were detected out of a total of 793 defectives.

In addition to oligophrenia and the urinary excretion of phenylpyruvic acid six cases presented features commonly associated with the disease. These included pallid complexion, fair hair and blue eyes, slight reduction of skull circumference, widening of the maxillæ, hyperreflexia and hyperkinetic movements of the fingers.

The remaining case combined mongoloid deficiency with phasic urinary excretion of phenylpyruvic acid.

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THERAPEUTIC PNEUMOTHORAX WITH CHEMOTHERAPY*

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IN 1953 A STUDY of the literature was made by the author,[1] in order to compare the results of pneumothorax and pneumoperitoneum in the treatment of pulmonary tuberculosis, on the objective bases of sputum conversion and cavity closure. This study also reported results in 275 cases of pulmonary tuberculosis treated initially by pneumothorax. Pneumothorax was shown to be superior to pneumoperitoneum as a method of achieving sputum conversion and cavity closure. Chemotherapy had been little used in the years covered by this study.

In 1955 a series of 499 cases of pulmonary tuberculosis, including the former 275, was reported by the author.[2] In all these cases pneumothorax was tried initially. The status of all cases was reported as on the fifth anniversary of pneumothorax induction. In this series too, chemotherapy was little used. Of 459 patients in whom pneumothorax was successfully induced 92.9% survived five years. The incidence of empyema was 7.1%, and the fatality rate from empyema, 1.4% of the whole series. It was felt that the observation of certain precautions in the management of pneumothorax had reduced the incidence of empyema, and that the five-year results were good. It was prophesied that with chemotherapy, pneumothorax, properly managed, would be safer and would return to popularity.

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The present study was undertaken to test the safety of therapeutic pneumothorax under the protection of chemotherapy.

SOURCE OF MATERIAL

Cases were provided by the following Ontario sanatoria (in no special order): Niagara Peninsula Sanatorium, Toronto Hospital for Tuberculosis, Beck Memorial Sanatorium, St. Lawrence Sanatorium, Mountain Sanatorium, Essex County Sanatorium, St. Mary-on-the-Lake Sanatorium, Sudbury Sanatorium and Brant Sanatorium.

The case records were abstracted on to a mimeographed form by the staffs of the various sanatoria and sent to the writer for analysis. A total of 124 cases was supplied.

COMPOSITION OF MATERIAL

There were 72 males and 52 females; the youngest was 18 years, the oldest 73 years; 78% were between 20 and 39 years of age.

Extent of disease was minimal in 21, moderately advanced in 49, advanced in 54 (N.T.A. classification); active A in 26, B in 78, C in 20, bilateral in 74, bacillary by any method in 107. A cavity was demonstrated in 80 and cavitation was multiple or there was a cavity over one inch (2.5 cm.) in diameter on the 14 x 17 inch radiograph in 29. Extrapulmonary tuberculosis was demonstrated in 9.

Associated chronic disease was reported in 14 cases, including diabetes in 5, and asthma, reactive depression, Bartholinian infection, psychosis, treated syphilis, alcoholism, Marfan's syndrome, and rheumatoid arthritis, each in one.

PERIOD OF OBSERVATION

Most cases came from the early years of chemotherapy. The observation period, starting from first induction of pneumothorax, was one year or less in 28 cases, one to two years in 43, two to three years in 22, three to four years in 18, four to five years in 8, and over five years in 5 cases (i.e. more than one year in 77%).

CHEMOTHERAPY

In only 42 cases was chemotherapy given continuously for one year or more. All other patients had single or repeated shorter courses, as was the custom in early years of chemotherapy. Fourteen had chemotherapy over a period of 90 days or less. The majority had PAS and streptomycin.

Chemotherapy was started 30 days or more before pneumothorax induction in 82 cases, less than 30 days before in 31, soon after induction in 7 cases, and more than 30 days after induction in 2 cases.

ADDITIONAL SURGICAL TREATMENT

Additional surgery was freely performed: pneumoperitoneum in 28 cases, thoracoplasty in 15, phrenic crush in 3, decortication in 5, pneumonolysis in 28, resection in 12. No surgical or collapse therapy other than pneumothorax was required in 68. In some cases more than one method was employed.

COURSE OF PNEUMOTHORAX TREATMENT

In 8 cases induction failed. In 84 cases pneumothorax treatment was discontinued for various reasons. In 32, refills were being continued at the last observation. Reasons for stopping refills included failure to check disease or to close the cavity, 7 cases; persistence of fluid, 8; resection, 3; empyema, 2; adhesions considered dangerous, 32; absence without leave, 1; hæmothorax, 1; fatal air embolism, 1; obliterative pleurisy, 3; atelectasis, 2; dyspnœa, 1; spontaneous pneumothorax, 1; refusal of treatment, 1.

Of the 116 inductions, only 43 were either continued to the end of observation or to completion of treatment, but 90 were continued for at least six months (77.5%). In two-thirds of these no further collapse therapy was required. Even when pneumothorax was continued for less than six months, no further collapse was used in half the cases.

Empyema developed in three cases. In one of these empyema occurred before chemotherapy was given. In another, chemotherapy was started only 10 days before pneumothorax was induced, and empyema developed three days later. In the third case, chemotherapy was given for seven weeks before induction and was stopped five weeks after induction, and empyema appeared six months later. In all three cases the disease was arrested. None of these cases had adequate protection by chemotherapy.

Persistence of fluid was not prevented by adequate chemotherapy in several cases.

RESULTS OF TREATMENT

In the 124 cases there were 4 deaths. One of these was traumatic and unrelated to tuber-

culosis. One was a cardiac death, one was from air embolism, and one from progressive tuberculosis. In 88 cases, disease was inactive or arrested at the end of the observation period.

DISCUSSION

In summary, our 124 cases included 54 advanced, 49 moderately advanced and 21 minimal cases. Of these, 77% were observed for more than a year. The results were: total mortality 3.2%, mortality due to tuberculosis 1.6%, incidence of empyema 2.4%; there was no mortality from empyema.

I believe that the incidence of empyema in this series is low, and give the credit for this to chemotherapy. I think the study suggests that some of the danger of pneumothorax treatment is removed by chemotherapy. Furthermore, in this series of cases chemotherapy was often inadequate by present standards. It seems reasonable to expect that, with more adequate chemotherapy, pneumothorax treatment will be found to be even safer than has been demonstrated here. Also it seems reasonable to expect the duration of pneumothorax treatment to be reduced by chemotherapy.

String adhesions, I believe, should still be cut, but band adhesions that permit satisfactory collapse of the diseased area perhaps need no longer be considered an indication for abandoning pneumothorax.

There is evidence in the literature[3, 4] that pneumothorax reduces the blood supply in the collapsed lung. This would tend to reduce the effectiveness of chemotherapy in the collapsed lung. So it would seem best to limit the usual use of pneumothorax and probably all collapse therapy to cases in which closure of a cavity must be the one aim of treatment. Pneumothorax should be discontinued when it is thought that this object has been achieved.

The writer suggests the use of pneumothorax in addition to chemotherapy: (1) In all cases with a cavity except when the cavity is very large, or when disease is extensive in both lungs, or when the lesion is very old. (2) In cases without a cavity, only when three months of chemotherapy with bed rest, including perhaps the use of posture or phrenic crush or pneumoperitoneum, has failed to give clear indication of diminishing the activity of disease and preventing cavity formation.

The most acute cases should certainly have one to three months of chemotherapy before pneumothorax is started. This is probably also true of cases of advanced disease, active in more than one area, but more than one month's preliminary chemotherapy is probably unnecessary for most cases. One month's preliminary chemotherapy is probably desirable in most cases.

Chemotherapy should be continuous for 12 to 24 months but pneumothorax might be discontinued when evidence of activity is absent, and probably 6 to 12 months of pneumothorax will usually be enough to ensure the closure of cavities and the prevention of cavity formation when chemotherapy is used.

The following contraindications to pneumothorax are suggested: (1) presence of persistent fluid above the dome of the diaphragm after three aspirations; (2) empyema; (3) adhesions preventing useful collapse of the diseased area; (4) cases without cavity, responding to chemotherapy in three months.

PLACE OF OTHER METHODS

It is not possible to indicate the place of pneumothorax in the modern treatment of tuberculosis without mention of other methods.

Thoracoplasty itself, it should be realized, always causes disability, and sometimes a total and permanent disability. The operation carries a mortality likely to be greater than that of pneumothorax given with chemotherapy. Thoracoplasty should be reserved for therapeutic failures by other methods.

Phrenic crush may sometimes be used as a preliminary to pneumothorax while chemotherapy is given.

Resection gives a good functional result, is all over quickly, and by removal of disease contributes to security from relapse. But short-term pneumothorax with long-term chemotherapy may give as good an end result with less risk, so I believe that pneumothorax should be tried first whenever possible. Resection may occasionally be preferable for persons whose temperament and circumstances cannot tolerate a longer period of treatment. I believe resection should never be used for cases of minimal extent. There may be a place for resection on the conclusion of pneumothorax treatment in a few cases.

Pneumoperitoneum may be used as a preliminary to pneumothorax when a three-month

course of chemotherapy is thought likely to be advisable before pneumothorax is induced, and when disease is active in both lungs.

CONCLUSION

On the basis of the results here reported, the writer feels that pneumothorax plus chemotherapy should be the preferred treatment for more cases of pulmonary tuberculosis than recent practice has favoured.

The writer is most grateful to the staffs of the several sanatoria for abstracting all these cases for him and making this report possible.

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Case Reports

SENSORY NEUROPATHY FOLLOWING CHICKENPOX*

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A PATIENT presenting an unusual neurological syndrome in association with varicella came under our care in February 1955, having been referred by Dr. J. G. Cock of Newmarket, Ontario. The nervous system manifestations were of a polyneuritic type not previously described. For this reason, and because the effect of treatment with adrenocorticotrophic hormone was carefully assessed, it was judged that report of the case would be of value.

Mrs. R.E., a 28-year-old housewife and mother of four children, was admitted to Ward G, Toronto General Hospital, on February 26, 1955, with a complaint of progressive unsteadiness in walking for six days. Her past health had been excellent. The only point of note was that since the age of 18 years she had had attacks of a peculiar allergic phenomenon manifested by transient swelling of the entire face, sometimes accompanied by urticaria-like lesions on the trunk. While she was in the Navy during the Second World War, this was fully investigated and no cause could be found. No attacks had occurred since the birth of her first child seven years ago. Her last child was born in December 1954, and since that time she complained of chronic fatigue which was compatible with her long and arduous work day.

On January 31 and on February 1, her two eldest children contracted chickenpox. On February 13, the patient herself developed an acute illness with aches and pains, sweating and chilly sensations and fever. By the next day the full-blown eruption of chickenpox was present, the vesicles covering the entire body and also involving the mouth and vagina. The constitutional symptoms subsided within 48 hours and the vesicles began to resolve. She got out of bed for the first time on February 19 and noted instability when on her feet and a sensation of stiffness of the upper trunk. She blamed these symptoms on her confinement to bed. On February 20, however, unsteadiness and weakness were more marked and on the 21st she was unable to walk. She noted weakness spreading to the trunk and arms and she became unable to turn herself over in bed. Beginning on February 21, she also noted the onset of paræsthesiæ, with numbness and tingling appearing first in the feet, then in the hands and spreading finally to the face. She began to have difficulty chewing her food; she noted an increase in salivation, and occasionally choked on attempting to swallow. Her limbs felt as if they were swollen and the entire mouth felt numb. She was often unaware of large food particles remaining in the mouth. The speech was slightly slurred and she blamed this upon difficulty in moving the lips.

Because of her failure to improve at home, she was admitted to hospital on February 26. She was a moderately obese young woman who had obvious difficulty moving about in bed. Her cheeks were of high colour. She was pleasant, co-operative and of above average intelligence. Scattered lesions of varicella covered the body; they were all dry and scaling and within a few days fell off. The general physical examination was normal except for an elevated blood pressure of 130/100 mm. Hg. The heart was not enlarged.

Her mental state was normal. Speech was slightly slurred. Examination of the cranial nerves revealed no abnormality; there was no nystagmus, no objective sensory changes within the mouth; the gag reflex was active and swallowing was well performed. Initially it was felt that there was moderate generalized muscular weakness, but this first examination was made immediately after a tiring trip and subsequent examinations revealed muscle power to be good. Tone was normal to hypotonic. There was moderate tenderness in the muscles, particularly about the shoulder girdle and in the calves.

There was very gross impairment in position sense in all four limbs and a resultant severe sensory ataxia. The finger-nose test was performed with much difficulty due to violent ataxia of the arms, equally severe with the eyes open or closed. There was no appreciation of gross movements in the fingers, and appreciation of movement at the wrist and elbow was grossly impaired. The heel-knee test could not be performed. Position sense in the legs was severely affected and even movements of small amplitude at the knee could not be appreciated. Initially, vibration sense was not impaired. Light touch, pain and temperature were everywhere normal. Two-point discrimination was well preserved, and figure writing was well appreciated in the hands. There was astereognosis in the hands due to the kinæsthetic sensory defect.

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All the deep tendon reflexes were absent, as were the abdominal reflexes. The plantar responses were very sluggish and the interpretation was equivocal. There was no disturbance in bladder or bowel function. She was quite unable to stand because of the severe ataxia, and could not sit up with any security. In this latter position a rhythmic tremor of the head and neck was seen, on which was superimposed the more irregular and wavering ataxia.

Routine urinalysis revealed no abnormality. The hæmoglobin value was 92%, the white cell count 11,100, and the sedimentation rate 4 mm. in one hour. Blood Wassermann reaction was normal. Lumbar puncture revealed a crystal-clear spinal fluid with an initial pressure of 120 mm. There were 15 lymphocytes per c.mm. The protein was 200 mg. %; sugar 54 mg. %; and chlorides 738 mg. %. The spinal fluid Wassermann reaction was negative and the colloidal gold curve flat. The electroencephalogram showed a mild diffuse dysrhythmia, without localizing features.

Because of the possibility that such nervous system manifestations as were seen in this case represented a neuro-allergic response to previous (virus) infection, and because ACTH and cortisone have been found of value in such reactions, treatment was begun with a daily intramuscular injection of 20 units of long-acting adrenocorticotrophic hormone (Duracton, Nordic Biochemicals Ltd.). The patient, very intelligent and observant, noted that paræsthesiæ in the fingers and about the mouth would appear about one hour after each injection, increase in severity during the day, and disappear before the next injection. We were inclined to agree with her that the medication was having an adverse effect and it was discontinued on the 12th day. Thereafter the diurnal exacerbation of these symptoms ceased.

During the subsequent month in hospital there was very little objective change in her condition. She was treated with a graduated series of exercises, and her joints were put through a full range of passive movement at least once daily. She noted frequent twitchings of her limbs and trunk, which we observed on several occasions. There were transient paræsthesiæ, mostly a tingling and numbness, about the mouth and in the fingers.

During the last week of March her condition appeared to deteriorate. This seemed to be due to continuing smouldering disease and increased anxiety about her condition. She complained of depression, malaise and a shaking feeling internally. There was increased twitching in her arms and considerable pain and stiffness appeared in the hands. The neurological examination at this time revealed the position sense to be grossly impaired as before. For the first time we were able to demonstrate a distinct loss of vibration sensibility in all limbs which was quite marked for a period of one week and then cleared partially until the vibration loss was only moderate and confined to the legs. Tenderness was very marked in the muscles of the hands, and the skin was hyperæsthetic; at the fingertips the slightest touch was painful and there was marked hyperalgesia to pinprick. A lumbar puncture was repeated and showed clear fluid with an initial pressure of 260 mm. There were five lymphocytes per c.mm., and the protein was 188 mg. %. The chloride and sugar levels were normal.

Again ACTH was started and again we found that this aggravated her symptoms. The drug was discontinued after four days. Slowly the pain and distressing paræsthesiæ subsided and during the last 10 days of her six weeks in hospital she remained fairly comfortable. At the time of her discharge from hospital the loss of position sense in all four limbs remained as grossly impaired as on admission. Ataxia, on testing, was slightly less marked and it appeared that training had resulted in more efficient, co-ordinate movement. There was slight impairment of vibration sense in the legs. There was marked hyperalgesia to pinprick in the fingertips. Light touch and temperature were everywhere well appreciated. Instability of the trunk and head was less marked and the tremor had disappeared. With eyes open she sat quite firmly but there was considerable ataxia with the eyes closed. Astereognosis remained in the hands. The deep tendon reflexes remained absent. Bladder and bowel function were, as ever, entirely normal. Power was good. She was quite unable to walk because of the ataxia.

It was our opinion that the patient would be many months convalescing and that there was a possibility of permanent disability, perhaps severe. Arrangements were made for her transfer by air to London, England, on Saturday, April 9.

DISCUSSION

The occurrence of neurological complications in varicella is rare. In 2,534 cases admitted to the Willard Parker Hospital from 1929 to 1933 inclusive, Bullowa and Wishik[1] found five cases of encephalitis, an incidence of only 0.2%. Among 6,774 cases admitted to the same hospital from 1941 to 1950, there were 18 cases of encephalitis, an incidence of 0.26%.

It has been known for many years that the commonest nervous system syndrome manifested in varicella encephalomyelitis is that of cerebellar disease with the production of a clinical picture of "cerebellar ataxia". Underwood's[2] comprehensive review of the literature up to 1935 revealed 119 cases of varicella encephalitis of which 30 were of this type. He noted that the cerebellar picture was very seldom pure but, more pertinent to our discussion, the complete cerebellar picture was often not present. Vertigo, for example, was present in only 13 cases, nystagmus in 12, and such features as Rombergism and adiadochokinesis were not as common as expected. Underwood mentions two cases as representative of fairly pure and undoubted cerebellar disease with explosive onset with vertigo, vomiting, marked prostration, and hypotonia. Other cases were not so distinctly cerebellar and we have been interested in the thought that some of the cases labelled "cerebellar ataxia" may have represented, at least in part, a sensory ataxia such as that seen in our patient.

Appelbaum *et al.*,[3] in their review of 59 cases of varicella encephalitis, state, "of particular interest was the occurrence of ataxia in 18 patients". The prominence of cerebellar signs in varicella encephalitis has been noted by others. In this series the occurrence of ataxia was much more common than other cerebellar signs which are usually associated. For instance, only seven patients showed nystagmus, six had slurred speech, four showed a positive Romberg sign,

and one had intention tremor. Kinæsthetic sensibility in the limbs was not recorded in this series.

In 1935, Walcott[4] described a case which was felt to be representative of the syndrome of cerebellar ataxia. The patient was a male child of three years who, on the seventh post-eruptive day, became so ataxic that he could not stand. No mention is made of vomiting. Examination revealed marked ataxia, coarse wagging movements of the head on sitting, lethargy, stolid facial appearance and neck stiffness. No specific note is made as to the sensory examination. There were no signs unquestionably of cerebellar origin, and the clinical picture, which resembles that of our case in some aspects, is equally compatible with a sensory ataxia.

The neuritic type of neurological complication is not common. Underwood dismissed such cases briefly with reference mostly to isolated mononeuritis, e.g. facial paresis, and the occasional case of polyneuritis (Guillain-Barré) to a striking degree. A good example is the second case reported by Masten.[5]

A case of particular interest is that of Lamy *et al.*[6] in a six-year-old child who developed pains in the legs on the sixth post-eruptive day followed by gross ataxia and refusal to walk. Examination revealed gross ataxia both with the eyes open and closed. There was weakness in the legs, the feet were cold, the muscles hypotonic, and there was hyperalgesia in the feet. There was decreased light touch sensation distally and absent leg reflexes. An electromyogram confirmed an abnormality in the peripheral neurone. The clinical picture, in their opinion, was one of polyradiculoneuritis with a secondary cerebellar syndrome to explain the marked ataxia. They do state that the ataxia could not be explained on the basis of a disturbance in deep sensibility or vestibular abnormality, but they do not specifically mention the testing of position and vibration sensibilities. It should be noted that none of the usual cerebellar signs accompanied the marked ataxia. Clinically their case resembles ours very closely.

The present case was characterized by extreme ataxia in the absence of other cerebellar symptoms. Examination revealed a profound loss of kinæsthetic sense in all limbs. Vibration sense was not affected at first, later became quite defective for a short while, and thereafter remained moderately impaired in the legs only. There was peripheral hyperalgesia and muscle tenderness suggesting some change in pain fibres, but there was never any decrease in cutaneous sensation to pain, temperature or touch. The sensory disturbance was largely one of impaired muscle and tendon sense with minor added disturbance in pain fibres. There were several features of the sensory change which were quite unlike a cortical sensory deficit.

It is our opinion that this case was one of polyradiculoneuritis following varicella, with the dominant pathological lesion confined to the posterior (sensory) nerve root and sensory nerve fibres in muscle. There were possibly further changes in sensory ganglia and posterior columns of spinal cord. We were impressed by the resemblance of this syndrome to cerebellar ataxia and have made the suggestion that some of the cases of "cerebellar ataxia" reported in the literature may represent, in fact, a sensory neuropathy in association with varicella.

A fair trial of therapy with ACTH was given, with no benefit. In fact, we noted subjective exacerbation of symptoms after each injection. Probably this treatment did not retard her recovery. During the six weeks that she was under our care it was disappointing to see no real evidence of improvement. It is anticipated that recovery will be prolonged and perhaps incomplete.

SUMMARY

1. A case of sensory neuropathy (posterior polyradiculoneuritis) following varicella is presented.

2. The syndrome of "cerebellar ataxia" following varicella is briefly discussed and it is suggested that some cases so reported may in fact be of the polyneuritic type.

3. Therapy with adrenocorticotrophic hormone was temporarily detrimental.

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ADDENDUM

The patient has returned to Canada since the submission of this report and has been re-examined as recently as March 21, 1956. She continued improving steadily and markedly until about December 1955, since

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when her condition has remained stationary. She walks without support but is quite ataxic and tends to stagger and clutch for support. There is only slight clumsiness of the hands and she does her own housework adequately. There is fairly severe residual sensory loss to vibration and passive movement in the feet and slight postural sensory impairment in the fingers. Cutaneous sensation is normal. Tendon jerks are absent.

SIMPLE DISLOCATION OF THE SUPERIOR TIBIO-FIBULAR JOINT

REPORT OF TWO CASES

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SIMPLE DISLOCATION of the head of the fibula is a rare injury. Macklin[1] in 1940 found 49 cases of dislocation of the head of the fibula in a review of the literature. Of these dislocations 40 were simple anterior or posterior dislocations unassociated with other injuries. He added two cases of his own. Since that time Vitt[2] has reported four cases, making a total of 46 cases. In view of the infrequency of this condition, the following two cases may be of interest.

CASE 1

W.S., a 17-year-old male, was being instructed in tumbling. As the patient was doing a hand spring over a vaulting horse, his foot caught in the mat, causing him to fall with his knee striking an interval between two mats. Apparently as he fell his knee flexed and was bent under him while his body twisted round.

The patient experienced immediate severe pain and was unable to walk. He was unable to fully extend his knee, and the head of the right fibula was very prominent and tender on pressure. Radiography revealed a dislocation of the right superior tibio-fibular joint (Fig. 1).

The region of the tibio-fibular joint was infiltrated with 2% procaine. The knee was flexed and the dislocated head of the fibula was reduced by pressing the head laterally and backwards. Reduction was confirmed by x-rays (Fig. 2). After the reduction the patient was treated by bed rest, with bathroom privileges only, for one week, after which time he was allowed to gradually increase his normal activities.

CASE 2

Mrs. B.P., aged 30, was admitted to hospital two days after falling on to the outer side of the right knee. The patient fell with the knees flexed; immediately after injury she experienced severe pain in relation to the outer side of the knee joint, and was unable to walk without assistance. During the first 24 hours after the accident the patient noticed numbness of the right foot followed by tingling of the toes. This cleared up spontaneously. On examination at the time of admission the head of the right fibula was very prominent and was tender on palpation. There was no loss of power or anæsthesia in the distribution of the lateral peroneal nerve. Radiographs confirmed the diagnosis of anterior dislocation of the head of the fibula (Fig. 3).

An attempt to reduce the dislocation under local anæsthesia was unsuccessful. Although it was possible to reduce the dislocation, the latter spontaneously recurred when the knee was extended. Consequently it was decided to perform an open reduction and fixation.

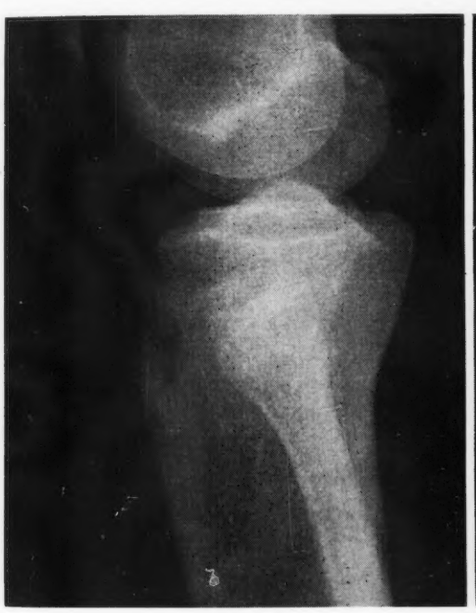

Fig. 1

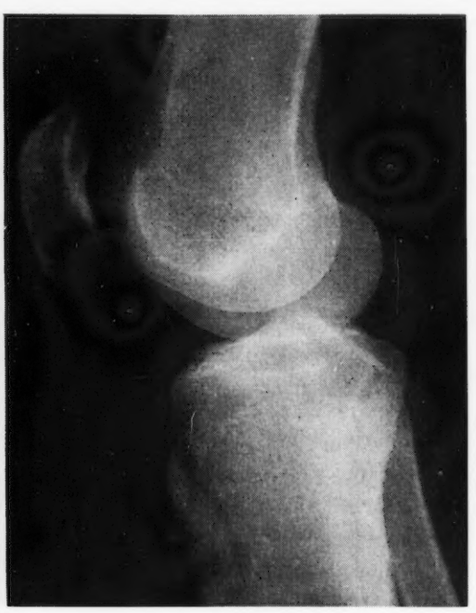

Fig. 2

Fig. 1.—(Case 1). Lateral view of right knee showing anterior dislocation of the head of the fibula. The oblique line of the fibular articular facets on the head of the tibia can be seen lying posterior to the head of the fibula. The head of the fibula lies more anterior than normally; this fact is not easily recognized unless this view is compared with a normal knee or with the post-reduction radiograph (Fig. 2). **Fig. 2.**—(Case 1). Post-reduction radiograph of the right knee.

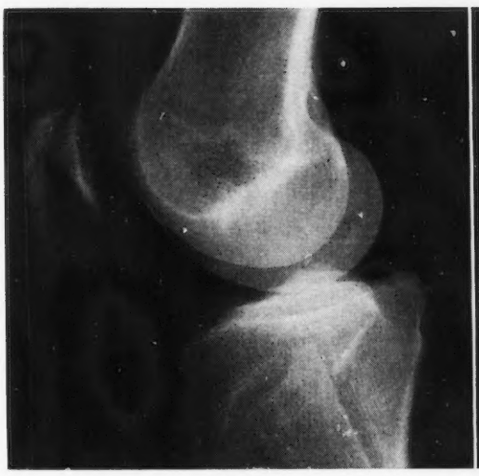

Fig. 3

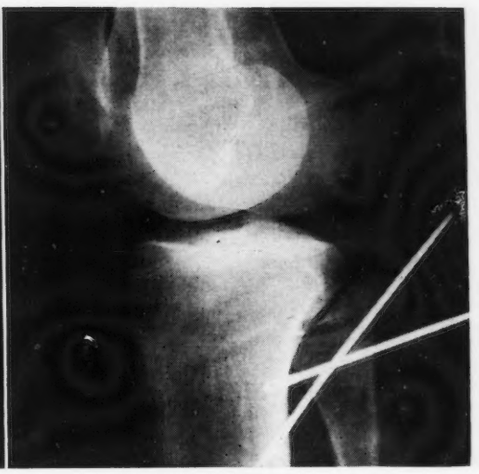

Fig. 4

Fig. 3.—(Case 2). Lateral radiographs of the knee to show anterior dislocation of the head of the fibula. **Fig. 4.**—(Case 2). Oblique view of the knee to show post-reduction position of head of fibula. The Kirschner wires are driven through the head of the fibula into the tibia below the level of the tibio-fibular joint.

The head of the fibula was reduced and held in position by means of two Kirschner wires transfixing the fibula and holding it to the tibia (Fig. 4).

DISCUSSION

The dislocation seems to result from a fall on the inverted extended foot. A sudden inversion strain causes tension on the peroneal muscles and may thereby dislocate the head of the fibula anteriorly. This is particularly likely to happen if at the time of the injury the knee is flexed, relaxing the biceps tendon and the lateral collateral ligament. A twisting motion of the body, externally rotating the tibia on the fixed foot, facilitates anterior dislocation of the head of the fibula.

At the time of injury, patients experience severe pain and are unable to walk on the injured leg. On examination the prominent head of the fibula can be seen and on palpation it is extremely tender.

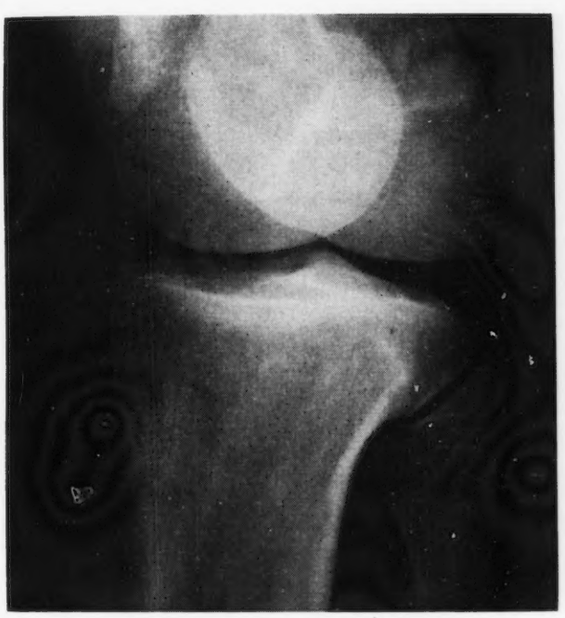

Fig. 5.—Oblique radiographs of the knee joint demonstrate the tibio-fibular joint very clearly and should be used in cases of dislocation of the head of the fibula where any doubt exists as to the diagnosis.

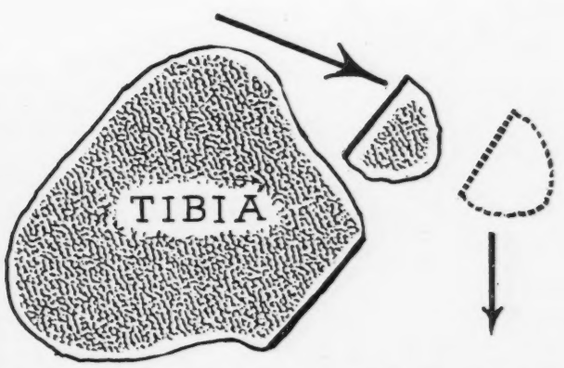

Fig. 6.—Diagram to show technique of reduction. The head of the fibula must first be pushed laterally in order to take it past the anterior edge of the fibular articular facet on the tibia. When the head of the fibula is free from this edge, it can then be pushed posteriorly and the reduction completed.

The dislocation can be seen on radiographs of the knee in the lateral view. However, *the lesion can easily be missed if the diagnosis is not suspected and if particular attention is not focused on the vague outline of the superior tibio-fibular articulation.* If the lesion is suspected, oblique views of the knee should be taken to demonstrate the tibio-fibular joint more clearly (Fig. 5).

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Reduction can usually be effected under local anæsthesia. The knee must be fully flexed, the foot everted, and direct pressure applied to the head of the fibula with the thumb. Lateral pressure must be applied first in order to displace the dislocated head of the fibula past the anterior edge of the fibular articular facet on the tibia (Fig. 6).

In the majority of cases, the joint appears to have been stable after reduction. In the second case reported in this paper the joint was not stable but reduction and fixation with two Kirschner wires appeared to be perfectly satisfactory. We could find no previous case reported in which the joint was not stable and required internal fixation.

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THREE CASES OF MEPROBAMATE POISONING*

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MEPROBAMATE (Equanil, Miltown), one of the new tranquillizing drugs, is now in wide general usage on this continent. The literature that is available to both the physician and the layman has emphasized the low toxicity of the drug, even when taken in large doses.[1, 2] However, recently three cases of meprobamate poisoning, with alarming and possibly near-fatal results, have come to our attention in this area. One case will be reported in some detail and the others briefly.

CASE 1

A 58-year-old woman was admitted to the Victoria General Hospital Psychiatric Unit on February 17, 1956, with a diagnosis of depressive reaction. She had a blood pressure of 190/90 mm. Hg, tortuosity of the peripheral vessels and arteriovenous nicking on fundoscopic examination. The patient had received five electroshock treatments as an outpatient. Meprobamate had been prescribed but she reported that she stopped taking the drug because it caused dizziness, nausea and vomiting.

Two days after admission she received an electroconvulsive treatment at 8.35 a.m. She had received phenobarbital, 60 mg. at 7.00 a.m.; atropine, 0.4 mg. i.m. at 7.45 a.m., and Sodium Pentothal, 450 mg. was given immediately before the electroconvulsive treatment.

In mid-afternoon, after being up and around for some time, she complained of drowsiness and retired to her room. At 4.00 p.m. it was noted that she could not be roused from her sleep and her blood pressure had dropped to 120/70. One hour later, the blood pressure had dropped to 80/60; respirations were 20 per minute and shallow, with little noticeable movement of the thorax; pulse was 72 and regular. The patient did not respond to painful stimuli but on occasion would open her eyes when her name was called. She appeared unable to move her limbs, which were flaccid. There seemed to be marked muscle relaxation. The patellar reflex was absent. There was no ankle clonus, Hoffman's sign, or plantar response.

The clinical picture appeared to be more like the toxic effects of a curare-like drug than barbiturate poisoning. A search of the patient's room revealed an empty vial which had contained meprobamate. As the only known cases of meprobamate intoxication had been treated by giving coffee and exercise, there was no precedent for treatment in this case.

The patient was given 250 c.c. of plasma extender i.v. and sodium caffeine benzoate, 450 mg. i.m., repeated in two hours. Within an hour of the onset of treatment, the blood pressure had risen to 120/80; respirations were 20 and deeper; the pulse was 70. One thousand c.c. of 5% glucose in water was started intravenously.

The patient now responded to questions by saying "yes" or "no". She was able to move her limbs voluntarily. An hour later, pulse, blood pressure and respirations were normal. The patellar reflex was present, but showed quick fatigue. The patient now admitted taking approximately 15 tablets, amounting to 6 grams. She reported that during the early stages of the reaction, she could hear her physician talking to her and could see him, but could not move her tongue or lips and she could not remember what happened later on.

Within 16 hours, her condition had returned to normal. Electroconvulsive treatment was resumed in two days. The patient was discharged on March 4 after six treatments.

CASE 2

A 56-year-old woman was discharged from hospital on January 12, after successful treatment for bronchopneumonia. A few days before discharge she became moody and withdrawn. On January 25, meprobamate, 400 mg. three times daily, was prescribed. On January

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We are indebted to Drs. R. J. Weil, M. G. Feener and N. G. Glen for their case material, and to Dr. D. Tonning, who supervised therapy in Case 1.

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27, six hours after the patient took approximately 25 pills, she was seen by her family physician. She was comatose, giving no response to pain. Breathing was shallow; reflexes were absent, heart sounds were faint and regular, with a rate of 60 per minute; systolic blood pressure was 40 mm. Hg.

She was given 5 c.c. of nikethamide (Coramine) i.v., then 1 c.c. of phenylephrine (Neosynephrine) i.v. The pulse became stronger and the blood pressure rose to 80 mm., but dropped in 15 minutes. Condition was unchanged 12 hours later, when the patient was hospitalized. On January 28 her condition was worse. Both lung bases showed coarse rales. Five c.c. of Coramine i.v. was given, followed by 500 c.c. of 5% glucose. A mercurial diuretic was administered i.m. and penicillin started.

At 5.00 a.m. on January 29 slight movements and moaning were noted. Improvement continued, so that the patient was fully conscious by noon and apparently none the worse for her experience.

CASE 3

A 39-year-old woman was placed on meprobamate, 400 mg. four times daily, for anxiety, on January 27, 1956. Physical examination was essentially negative. Blood pressure was 100/80 and the pulse 80. On January 31, 1956, the dosage was reduced to one tablet twice daily because of drowsiness. She was also taking phenobarbital, 8 mg. 4 times daily. At 10 p.m., February 1, she phoned her physician, telling him in a very slurred voice that she had taken all her meprobamate tablets. At 10.15 p.m. she could not be roused. Her pupils were small and her eyes wandering from side to side. As she was being placed in the ambulance shortly afterwards, she suddenly became very excited and violent. Chlorpromazine, 25 mg. was given i.m. as a sedative at 10.30 p.m. Half an hour later the patient appeared more calm, and discussed some of her emotional problems. Strong suicidal feelings were elicited. At about 11.30 p.m., the patient became semi-comatose. The stomach was washed out and a quart of warm, strong coffee was left in the stomach. Adrenaline was given i.m.

During the eight hours after admission, the patient gradually improved, so that on the morning of February 2, she felt her usual self, except for some drowsiness. The lowest blood pressure reading in hospital was 100 mm. systolic, the highest 142. The pulse was 112 on admission and 76 by next morning. A routine blood picture revealed no abnormalities. It was estimated that the patient had taken 6-18 tablets.

SUMMARY

Three cases of toxic reaction from overdosage of meprobamate are presented. The main features from this small series appear to be coma, marked muscle relaxation with absent reflexes, a dangerous fall in blood pressure in two of the cases, and quick recovery without sequelæ. The reactions suggest that a greater dosage might well cause death. Meprobamate must be prescribed with care in potentially suicidal patients. Thus far, no definite regimen of therapy has been developed.

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CHRONIC ADULT PORPHYRIA*

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PORPHYRIA is a constitutional anomaly which may occur early or late in life. It is manifested by a variety of symptoms which include bullous formations on the skin (precipitated by heat, light, and mild trauma), pigmentation and scarring, neuropathies leading to actual paralysis, and various psychoses. All of these are at some time or another accompanied by the presence of reddish-coloured urine which fluoresces when exposed to Wood-filtered ultraviolet light.

Dermatologists as well as other clinicians should become more aware of the significance of these findings. A. J. Kergin[1] recently reported three cases of acute intermittent porphyria, stressing the need for the surgeon to have a high index of suspicion in cases which might simulate surgical disease. Brunsting *et al.*[2] in 1950 recorded 21 cases of chronic porphyria with cutaneous manifestations, in adults. They were observed in the Mayo Clinic over the previous 5-6 years. Seventeen of these cases are reviewed in detail and emphasis is placed on hepatotoxins, chiefly alcohol, as precipitating factors. These workers believe the disease to be commoner than is generally supposed.

According to Duncan[3] the porphyrins are chemical compounds participating in normal pigment metabolism and present throughout the plant and animal world. All porphyrins have a common basic chemical structure, the porphyrin nucleus, composed of four pyrrole rings united by four additional carbon atoms. The porphyrin nucleus is the basis for the structure

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CLASSIFICATION OF PORPHYRINS (WATSON[4])

Type and incidence	*Clinical*	*Chemical*
1. Congenital (rare) photosensitive.	Onset early in life—prenatal or somewhat more commonly postnatal. Hydroa aestivale: eventual scarring and mutilation of the exposed skin—erythrodontia. Splenomegaly and hæmolytic anæmia not infrequent; splenectomy may relieve and cause porphyria to become latent, with disappearance of photosensitivity.	Absence of Ehrlich-reacting porphobilinogen in urine. Large amounts of uroporphyrin and coproporphyrin in urine. Slight or negative excretion of zinc complex.
2. Acute intermittent (relatively common).	Somewhat more common in females. Abdominal pain of various types. Peripheral neuropathy with pain in extremities. Varying neuropsychiatric disturbances: weakness, paralysis, hysterical behaviour or outspoken psychoses. Pigmentation of skin in some cases.	Porphobilinogen usually present in urine at least during acute attacks. Small amounts of uroporphyrin (zinc complex).
3. Mixed (cutaneous), (relatively uncommon).	Late appearance of photosensitivity (so-called cutanea tarda). Liver disease or functional impairment frequent. Attacks of abdominal pain; neuropsychiatric disturbances infrequent.	Porphobilinogen inconstant. Varying appearance of uro-type porphyrin with various mixtures of coproporphyrins I and III.

of hæmoglobin, bile pigments, chlorophyll, myoglobin, and cytochrome, a respiratory enzyme. Since the porphyrin nucleus constitutes an essential part of the respiratory enzyme, they must be present in every cell of the body. Goldstone of the University of Pennsylvania states that of all the porphyrins only three are produced endogenously. They are uroporphyrin, coproporphyrin and protoporphyrin.

C. J. Watson[4] classifies the porphyrins, with description of the various features, as shown above.

A simple qualitative procedure to determine the presence of porphyrins in the urine is as follows: (1) Acidify the urine with hydrochloric acid and examine for fluorescence under the Wood filter light. Fluorescence means that porphyrins are present. (2) Acidify a second sample of urine with acetic acid and extract with ether. This removes coproporphyrin, which is ether-soluble. If the aqueous layer still fluoresces, uroporphyrin is present. (3) Another portion of urine is tested for porphobilinogen by the Watson-Schwartz reaction. Mix equal parts of urine with Ehrlich's reagent in a test-tube. To the mixture add an equal volume of saturated aqueous sodium acetate. A few c.c. of chloroform is then added. The aldehyde compound of porphobilinogen remains in the aqueous fraction, while that of urobilinogen is completely extracted with chloroform. This is pathognomonic of porphyria, present in acute intermittent porphyria.

Mrs. R.H., aged 70 years, consulted me on December 3, 1953, because of recurrent blisters on the backs of both hands and arms, first noticed in September 1953. She stated that her skin began to darken and pigment after hospitalization for a phlebitis in the right lower leg in April 1953. Coincident with pigmentation there developed an accentuation of hair growth, which had slowly been increasing in the last few years. These blisters occurred with slight trauma and seemed to a lesser extent to be induced by exposure to sunlight. They progressed to minimal scarring with periodic recurrent flare-up. She consulted an internist on the advice of her private physician, and was hospitalized on May 29, 1953. Her complaints at this time were of: (1) weakness and "dragginess" of several weeks' duration; (2) loss of weight; (3) soreness of body, particularly the right arm and hips, which had persisted since she spent four weeks in bed for her phlebitis; (4) gradually increasing discoloration of the skin and increasing growth of hair on the face and forehead, a source of great concern to her.

A history was obtained, at this time, of an injury to the right knee two years previously, removal of appendix at the age of 40, and tonsillectomy at the age of 60. Family history was essentially negative. She had an irritation of her eyes, some disturbance of hearing, and chronic gastric complaints with episodes of distress associated with spasticity or gas formation. No history of ingestion of drugs was obtained. During her stay in hospital the thrombophlebitis in her right leg flared up for a few days and then improved. Urinalysis was negative. Blood examination revealed normal N.P.N. and fasting blood sugar; sedimentation rate, 97 mm. in an hour; hæmoglobin 9.65 g. %; red cell count 2,930,000; white cell count 5,600; differential normal; basal metabolic rate minus 3%; chest radiography, intravenous pyelography, gastrointestinal series and barium enema all negative. Tests for adrenal insufficiency were consistent with normal function. Pelvic examination revealed a small uterine nodule suspicious of fibroid.

I advised immediate hospitalization for further studies but the patient did not return until February 10,

1954, at which date she was admitted to Victoria Hospital. History now revealed that since her previous investigation she had suffered from severe constipation and intermittent aches and pains. In September 1953 blisters began to develop on the backs of the hands and arms. This seemed to be related to sunlight and slight injury to the skin. Pigmentation had deepened and hair growth to the face continued to increase, especially along the hairline of the forehead and either side of the face. The broken areas of the skin healed, leaving scars with milia formation. The urine had taken on a wine colour. She denied alcoholic ingestion and gave no history of familial involvement.

Laboratory Investigation

The urine fluoresced markedly with Wood's filter lamp, and was strongly positive for coproporphyrin by the Watson-Schwartz reaction, but negative for porphobilinogen. Hæmoglobin value was now 90%; red cell count 3,930,000; colour index 1 (vitamin B_{12} injections had been administered since the previous blood test); sedimentation rate 14 in one hour; 17-ketosteroid excretion was again found to be normal. Urine was negative for sugar; no pathogens were found on examination of bacterial flora of the stools. Bilirubin and thymol turbidity tests were within normal limits. Bromsulphalein tests showed 27% retention in 45 minutes; the cephalin flocculation test was negative. The glucose tolerance test showed a diabetic type of response. A skin biopsy was reported on as follows: "The epidermis is atrophic. Hyperkeratosis is not seen. There is considerable liquefaction degeneration in the deeper layers of the epidermis but the most outstanding feature is the increased fragmentation of the basal layer and deeper layers of the stratum spinosum with brownish-black pigment (melanin). The collagen in the superficial corium tends to be clumped and is fragmented and faintly basophilic. The atrophy of the epidermis and changes in the collagen may be so-called senile changes. The vascularity of the corium is meagre. Occasional lymphocytes are seen about hair follicles but the lesion in the skin is not primarily inflammatory. Changes in the skin make one think of the late stages of pellagra. No specific pathological changes are seen."

During her 10 days in the hospital she was placed on a low fat, low carbohydrate diet, and vitamin B_{12} was administered intramuscularly. The bullous lesions disappeared and her general health improved. An attempt was made to reproduce blistering with ultraviolet light but was unsuccessful. She was discharged from hospital with advice to avoid trauma, sunlight, barbiturates and alcohol in any form. Injections of vitamin B_{12} were to be continued.

She was not seen again until May 23, 1954, at which time she reported no further recurrence of bullæ and no other essential change in her condition except for considerable loss of weight. Coloured urine was still present which fluoresced when exposed to the Wood filter lamp and porphyrins were again present on qualitative analysis. In view of her weight loss she was allowed to return to a normal diet. She had now become reconciled to her appearance and, since the condition had become stationary and was essentially benign, no further treatment was prescribed other than that previously advised, with continuation of the vitamin B_{12} injections to be carried out under the care of her physician.

DISCUSSION

This case fits acceptably into Brunsting's group of the so-called chronic adult porphyrias. This woman had bullous lesions of the hands on exposure to light or trauma, resulting in scarring with milia formation, melanosis, hypertrichosis and vague abdominal symptoms. The coloured urine with positive test for porphyrins is pathognomonic. A high glucose tolerance test suggestive of diabetes but with urine and blood sugar studies negative, and with a bromsulphalein retention test of 27%, rather favours liver dysfunction. What part the infective thrombophlebitis played as a toxic focus to damage the liver is highly speculative. The failure to reproduce bullous lesions by ultraviolet light is significant. The association between porphyrins in urine and photosensitivity is not at all clear and offers a fruitful field for experimental investigation. The future holds much in store for the elucidation of this problem.

The administration of vitamin B_{12} with a low fat, low carbohydrate diet improved her general health and prevented further appearance of bullæ. The treatment in general for the cutanea tarda type is to combat the precipitating factors such as bile obstruction, hepatitis, diabetes or alcoholism. Schrumpf[5] observed a latent form of porphyria with marked bullous formation on exposed parts of the body in a patient aged 28 years during her second pregnancy. She was treated by dimercaprol (BAL) with distinct improvement; regression of skin and of urinary changes suggested that BAL may be of benefit in porphyria.

No rational treatment of congenital porphyria has so far been possible. In Watson's classification he speaks of the value of splenectomy. Gray and Neuberger[6] reported slightly increased excretion of porphyrins but no change in sensitivity to light or in hæmatological findings after splenectomy.

SUMMARY

1. A case of chronic adult porphyria (cutanea tarda type) is reported.

2. Recent literature reveals that this condition may occur more frequently than is suspected.

3. Dermatologists are in a favoured position to discover such cases, especially when the latter have cutaneous manifestations, and perhaps to shed further light on the complex problem of porphyria.

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REVIEW ARTICLE

A REVIEW OF NORMAL CALCIUM AND PHOSPHORUS METABOLISM

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FOREWORD

OUR INVESTIGATIVE UNIT has been interested in the metabolism of calcium and phosphorus for a number of years, and we have come to realize that no one medical text or journal renders an easily comprehensible, complete and yet concise review of the subject. We feel that a precise account of this subject may be of service to others, both in stimulating interest in the field and in providing an adequate reference list.

It is hoped that this paper dealing with the metabolism of calcium and phosphorus in normal people, and following the outline listed below, will pave the way for a discussion, subsequently to be published, on the etiology, pathogenesis, and treatment of hypercalcæmia and hypocalcæmia.

The values for calcium and phosphorus are expressed in mg. % rather than in mEq./l. The reason for this is that the valence of phosphorus varies, and therefore the normal ranges for phosphorus in mEq./l. could have many values, with resulting confusion.

OUTLINE OF REVIEW

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I. DISTRIBUTION AND PHYSIOLOGICAL EFFECTS OF BODY CALCIUM

A. The *bones* and *teeth* contain about 99% of the body calcium but the 1% found in body fluids exerts important physiological effects. Over 90% is found in the skeleton as calcium phosphate and calcium carbonate. Calcium carbonate and to a lesser extent calcium acid phosphate and calcium hydroxide are adsorbed on a nucleus of calcium phosphate.

Sixty per cent[1] of the neonatal skeletal calcium is deposited in the last two months of pregnancy and it is at this time that the maternal calcium intake should be raised. From the time of cessation of skeletal growth until death, the bones gradually become richer in carbonate and poorer in phosphate. This results in increased brittleness. However, whether new bone is formed or bone resorption occurs, the calcium/phosphorus ratio in bone has always been found to be about 2.15.

While it is not the purpose of this paper to discuss bone formation and resorption in detail, it may be briefly stated that bone develops: (a) from cartilage—"endochondral bone formation", (b) from embryonic mesenchymal tissue directly—"membranous bone formation", and (c) on already formed bone—"endosteal bone formation".

During skeletal development and after the cessation of normal skeletal growth, bone is constantly being reabsorbed and reformed in a dynamic balance. The osteoblastic cells secrete a protein matrix which surrounds these cells; and they elaborate the enzyme alkaline phosphatase, which releases inorganic phosphorus from organic phosphate esters. This serves to raise the calcium and phosphorus above its saturation point, and results in their precipitation on the osteoid material to form part of the apatite structure of bone. The exact role of the osteoclastic cells is not clear. They probably reabsorb bone directly and also act as scavengers to clear up the resulting debris.

To maintain a normal balance between bone formation and reabsorption, normal tissue and plasma concentrations of calcium and phosphorus are essential. This is brought about by the adequate intake of calcium, phosphorus, the vitamins D, C, and A, and the normal function of the parathyroid, renal and respiratory organs. An increased local acidity or magnesium concentration tends to inhibit ossification. Vitamin C is needed for the normal development and activity of the osteoblasts. Vitamin A is somehow involved in the balanced control of osteoblastic and osteoclastic activity. The action of vitamin D will be dealt with later.

The precise constitution of the apatite bone structure is unknown and it is still a matter of controversy. Many formulæ have been given and their significance has been commented upon by Armstrong.[2] The composition and structure of bone salts appear to be quite variable in different areas and under different circumstances. This variation is due in part to the large and very active surface of the bone mineral crystal, to which carbonate, phosphate, bicarbonate, fluoride, sodium, potassium, magnesium, citrate, and other ions are interchangeably attached. For a more complete discussion the reader is referred to the works of Shear and Kramer[3] and Hodge.[4]

The view that calcification of osteoid material is based purely on the mechanism of calcium and phosphorus solubility product ($Ca \times P = K \pm 35$) above the saturation point of extracellular fluid has been challenged. Waldman[5] has demonstrated that even after boiling or treatment with heavy metals, rachitic cartilage will accumulate mineral deposits if immersed long enough in a fluid with a high concentra-

tion of calcium and inorganic phosphate. They also showed that the bone salt is not diffusely precipitated but occurs in those areas where deposition will normally take place. Sobel[6] has shown the same to take place in bone previously made rachitic by beryllium or strontium. These experiments seem to indicate that an apatite structure in normal bone may be deposited *in vivo* without the action of enzymes or other active cell functions. However, cell activity *in vivo* is likely, since calcium in the above experiments was deposited only in areas where organic matrix already present is normally calcifiable; and enzymes and other constituents of cells must be responsible for the formation of this matrix. Also the *in vitro* experiments were carried out in a medium with a much higher concentration of salts than occurs in body fluids.

In endochondral bone formation, the swollen hypertrophied cartilage cells are associated with a large storage of glycogen, and just before mineralization occurs, these stores disappear or are greatly diminished. Because of this observation, Harris postulated a relationship between the breakdown of glycogen (via the glycolysis cycle[7]) and bone mineralization. This involves the uptake of phosphorus from tissue fluid so that glucose, fructose, etc., subsequently formed must be phosphorylated. When the pyruvic stage is approached, it was postulated that alkaline phosphatase acted to release inorganic phosphorus and much energy in accordance with Robison's theory.[8] Hence instead of the inorganic phosphorus of the tissue fluid being directly incorporated into the apatite structure, it first underwent attachment to sugars. These ideas seem to have been reinforced by work done with phlorizin, iodoacetate and fluorides which are known to be selective inhibitors in certain specific stages of glycogenolysis and glycolysis in liver, muscle and other tissues. Gutman, Warrick and Yü,[9-11] using 10^{-2}M phlorizin which inhibits phosphorylase present in cartilage,[12] produced a block in the *in vitro* calcification of cartilage. The addition of inorganic phosphorus was ineffective, but calcification recommenced when the block had been by-passed by adding to the medium substances such as glucose-1-phosphate, fructose-6-phosphate, or any of the other intermediates formed in glycolysis except unphosphorylated pyruvic acid.

Robison and Rosenheim[13] have shown a similar effect when 10^{-3}M iodoacetate, which inhibits 1,3-diphosphoglyceric aldehyde dehydrogenase, is added. Calcification only recommenced when this block had been by-passed by adding to the medium 3-phosphoglycerate or dihydroxy-acetone-phosphate. Also it has been shown by Robison and Rosenheim[13] that 10^{-4}M fluoride when added blocked the *in vitro* calcification of cartilage when inorganic phosphorus was present. Fluoride blocks the formation of phosphopyruvate from 2-phosphoglycerate. For a better understanding of the blocking action, the reader should have before him a picture of the glycolysis cycle. This may be obtained from any medical or biochemistry text.

Marks and Shorr[14] have digested glucose present in cartilage cells with ptyalin and prevented the *in vitro* calcification of cartilage. This is another piece of confirmatory work.

As for the matrix, the development of the property of calcifiability seems to be closely tied in with alterations in the stage of the acid mucopolysaccharides, chiefly chondroitin sulphates,[15] and perhaps of collagen which is present in the matrix ground substance. The collagen and chondroitin sulphuric acid become associated with much calcium[16] in a not clearly understood fashion, before actual calcification occurs. Then phosphate is released via glycolysis from within or about the matrix cells, and with calcium the apatite structure is evolved. The mechanism whereby the other bone minerals are laid down is as yet unknown.

In summary, the above observations on cartilage cells and matrix before calcification seem to imply a much more complex mechanism than the simple idea of the precipitation of a calcium phosphate, either directly from a fluid supersaturated with respect to calcium and phosphate ions, or indirectly as the result of the liberation of inorganic phosphate from phosphoric esters through the action of a single enzyme alkaline phosphatase. Therefore a complex of calcium, chondroitin sulphate, collagen and phosphorus and other minerals is built up and at the right time and place, by molecular rearrangements, the apatite structure is evolved.

Recent work has shown that alkaline phosphatase is inhibited by beryllium which blocks glycolysis at the beta-glycerophosphate stage. Also, this enzyme may play a partial role in conferring the property of calcifiability of organic matrix, since it has been shown to play a part in the synthesis of the fibrous proteins present in matrix.[17-19] Myerhof and Green[20] have shown the enzyme to play a significant role in catalyzing transphosphorylation and the synthesis of phosphoric esters.

Gutman[21] has been careful to point out that the newer ideas on "endochondral bone salt formation", while yet not clearly understood, may not apply to "endosteal bone formation".

The so-called "simple" calcium x phosphorus solubility product certainly seems to follow physico-chemical laws as far as the plasma and tissue fluids are concerned, for in most cases a drop in one element is followed by a rise in the other. In addition, undersaturation or supersaturation of this product may inhibit or speed up whatever complicated enzyme reactions occur in bone salt formation. Indeed, we have seen that normal calcification can take place in the *in vitro* experiments on bone with solutions of high concentration of calcium and phosphorus. Also in disease, many symptoms and signs, including bone disturbances and metastatic calcifications, can be explained upon the degree of saturation in tissue fluids of these two elements. Hence it would still seem that, until the whole subject has been fully cleared up, the calcium x phosphorus product provides us with a simple index, if only an indirect one, of what is going on and what we may expect to see in pathological states.

Yendt, Connor, and Eager Howard[22] subjected 58 human sera to ultrafiltration studies and tested their ability to calcify rachitic rat cartilage. These sera were obtained from normal subjects as well as from those in whom, for various reasons, either the serum calcium or phosphorus level was elevated. The serum from patients without azotæmia nearly always produced calcification when the product of the calcium expressed as mg. % x the concentration of the phosphorus expressed as mg. % in the serum ultrafiltrate was 34 or more. The sera obtained from patients with chronic renal insufficiency usually did not produce calcification until the Ca x P product of the ultrafiltrate was 55 or

more. It seems that perhaps an elevated serum magnesium and other factors as yet unknown play a causative role. An elevated urea or lowered serum sodium, chloride or bicarbonate did not appear to inhibit the process.

B. *Plasma* contains about 9-11.5 mg. % (4.5-5.5 mEq./l.) of calcium. Since the red cells contain only minute amounts, whole blood is found to contain 4.5-6 mg. %. Lymph, cerebrospinal fluid, aqueous humor, ascitic and œdema fluid contain it in somewhat lesser concentrations. The fetal plasma at term contains 11-12 mg. % and the maternal plasma calcium level is about 8.5-9.5 mg. %. During infancy and early childhood the average values approach the upper limit of the range, decreasing with advancing years.

The plasma calcium may be divided into a diffusible portion of 5-6.5 mg. % and a non-diffusible portion of 4-5 mg. %. The non-diffusible fraction depends upon the plasma protein concentration, especially the albumins, in the proportion of about 0.84 mg. per gram of protein. Therefore a determination of the total plasma calcium may be meaningless unless it is interpreted in relation to the plasma protein concentration. Thus when extensive proteinuria occurs, the fall in the plasma calcium level consists essentially of a decrease in the non-diffusible fraction and is mainly due to a reduction in the plasma albumins.

The diffusible plasma calcium may be divided into a non-ionized portion of about 0.25 mg. %, which consists of insoluble colloidal calcium salts of citrate, phosphate, etc. The rest is ionized and amounts to 4.75-6.25 mg. %. It is the physiologically active fraction.

With the oral ingestion of calcium, the plasma level rises to a maximum in 2-3 hours and is normal in 4 hours. Intravenous administration of calcium results in a maximal level in a few moments with a return to normal in 1-2 hours. Intramuscular administration as calcium gluconate produces a maximum plasma level in about 1-2 hours with a return to normal levels in 3-4 hours.

When the exogenous administration of calcium fails to prevent tetanic manifestations due to hypocalcæmic states, it is unwise to administer magnesium parenterally, for the latter element only serves to further lower the plasma ionized calcium level and may precipitate acute tetany.[23]

The plasma calcium level varies directly with the concentration of plasma proteins and with the hydrogen ion concentration, and it varies inversely with the concentration of the plasma phosphorus. The latter is influenced by parathyroid hormone. When the factors affecting calcium and phosphorus metabolism are constant except for the amount of parathyroid hormone, the relationship of the calcium to the plasma phosphorus is such that the product of their values in mg. % is nearly a constant, K (K = 35). This solubility product can change, however, when the other factors such as kidney disease, pH, and CO_2 tension affecting calcium and phosphorus metabolism are not constant and may represent a state of supersaturation or undersaturation in reference to the true solubility product.

McLean and Hastings[24] have put forward another idea. They claim that the ionization of calcium in body fluids is primarily determined by an equilibrium between calcium and protein. They consider that calcium in protein containing fluids is present as a calcium proteinate, which ionizes as a weak electrolyte into calcium and protein ions with a residue of protein-bound calcium, i.e. of the non-diffusible fraction. They have devised nomograms so that the concentration of ionized calcium can be read from curves made up by plotting the plasma protein concentration and the total plasma calcium levels against analyzed ionized calcium values.

C. Another important role of intravascular ionized calcium is in *Blood Coagulation.* It may be replaced in this capacity, but less efficiently, by strontium or barium, and hardly at all by magnesium. The ionized calcium is required for the formation of thrombin from its inactive precursors in the blood and tissues.[25]

D. Calcium diminishes *Cell Membrane Permeability.* Since cells are normally impervious to calcium, the action of calcium is probably exerted at the cell surface. It seems to be one factor in stabilizing surface colloidal systems and therefore in diminishing cell membrane permeability. Sodium and potassium have an opposite effect in this connection, producing an increased cell permeability and colloidal dispersion. A balance of these and other ions is needed for normal cell function.

There is no evidence that injections of calcium will decrease capillary wall permeability; consequently it would seem to be of little value in cases of angioneurotic œdema, or effusions such as pleurisy, or in other inflammatory conditions.

E. *Muscle* has about 8 mg. of calcium per 100 grams of wet weight. Its irritability is enhanced by an increased sodium and/or potassium ion concentration and by a diminished calcium, magnesium or hydrogen ion concentration,

$$\text{irritability} \propto \frac{(Na^{+}) + (K^{+})}{(Ca^{++}) + (Mg^{++}) + (H^{+})}$$

The exact site of action of these ions is still questionable. Peripheral nerves seem to be mainly involved. The twitchings of muscles in tetany disappear after cord transection.[26] Therefore the whole reflex arc (which includes the cord itself) and the neuromuscular junction obviously are involved.

Raised calcium ion levels tend to inhibit *Skeletal, Unstriated Muscle,* and the *Voluntary* and *Autonomic Nervous Systems.* Decreased plasma calcium causes an increased neuromuscular irritability with twitchings (tetany) and

in advanced stages convulsions. The heart and uterus are exceptions.

Autonomic ganglion cells are stimulated by a decreased plasma and tissue calcium concentration so that these cells are more readily irritated or discharged by a given amount of acetylcholine. Contrariwise, high calcium concentrations block ganglion as well as neuromuscular transmission.[1, 27-29]

The action of calcium on the heart may show parasympathetic or sympathetic effects. In early perfusion experiments potassium and calcium were found to exert antagonistic effects on the heart. Mazia[30] in 1941 showed that the antagonism is due to the displacement of one cation by the other at a critical concentration ratio of these two elements.

A decrease in the calcium concentration produces effects characteristic of potassium excess. If the calcium drop is sufficient, the heart will stop beating in diastole. When the calcium level rises, more forceful contractions of the myocardium develop. The degree of diastole progressively diminishes until arrest occurs with systolic standstill (calcium rigor).

It is not certain where calcium and potassium exert their effects—whether it be on the cardiac nerves, the coronary arteries, the myocardial fibres, or the conduction system.[31]

Hoff[32] in 1939, perfusing hearts with a gradually increasing calcium concentration, showed an initial bradycardia in the electrocardiogram at levels of 15-35 mg. %. This may be due to a compensatory vagal action. Between 30 and 60 mg. %, ventricular fibrillation set in, and cardiac arrest developed when the calcium level went above 60 mg. %. In humans, signs of vagal action are evidenced by a bradycardia, sinus arrhythmia, a shifting pacemaker and various degrees of heart block. At higher concentrations the ventricular muscle becomes so irritated that foci of idiopathic ventricular rhythm and ventricular extrasystoles are seen in the electrocardiographic recordings.[33]

In some ways the action of calcium seems to resemble that of digitalis, and the question arises whether it is wise to administer calcium intravenously to such patients, should the need arise. Experimental evidence[34] does not suggest a summation of effects of these two drugs.

The effect of calcium on *uterine* muscle seems to be similar to that on the heart. Danforth and Ivy[35] showed that in post-partum animals when the ionized calcium content was low, the activity of this muscle tissue was greatly diminished. It was also relatively insensitive to the effect of oxytocic drugs. They suggested that in post-partum cases where oxytocic drugs had little effect in increasing the uterine contractions, the administration of calcium might be very useful.

Bauer[36] claims that, because of the antispasmodic action of calcium, the intravenous administration of calcium is useful in relieving gallbladder, renal and intestinal colic. Trattner and Walzak[37] have reported that muscle spasm of the renal pelves, calices, ureters and bladder can be reduced in a high proportion of patients by administering 10 c.c. of 10% calcium gluconate intravenously.

F. About 150 mg. % of calcium is excreted in the *urine* per 24 hours and 0.4-0.8 gram is lost in the stools. These routes of excretion will be discussed at greater length under the heading of "calcium excretion".

G. It should be briefly mentioned that *human milk* is obviously rich in calcium, as is cow's milk. During a normal lactation period over 80 grams of calcium may be lost. The actual content of calcium in human milk is less than in cow's milk, but more of it is in an easily absorbable form.

II. Distribution and the Physiological Importance of Phosphorus

Like calcium, phosphorus has many functions and it is widely distributed in the body.

Its concentration in the plasma is highest in the summer and lowest in the winter. It seems to vary with the concentration of ultraviolet light. This is probably explained by the fact that ultraviolet rays increase absorption of calcium, allowing more free soluble phosphorus to be absorbed. Curiously enough, magnesium when injected tends to lower not only the plasma calcium but also the phosphorus concentration. While it is known that insulin, which increases carbohydrate utilization, is associated with a drop in plasma phosphorus and potassium lasting for 4-5 hours in the case of crystalline insulin, it is difficult to see why the injection of epinephrine results in similar changes.

The urine and stools per 24 hours each contain about 1 gram of phosphorus. A more detailed discussion of this will follow.

The inorganic form exists as an electrolyte component of intracellular fluid and urine. It exists as the ions of monobasic and dibasic salts of orthophosphoric acid. The actual proportions of these two salts vary with the pH of the internal milieu and play an important role in the body's acid-base balance. The inorganic form is present in the complex apatite mineral structure of bone. Inorganic phosphorus takes part in the formation of complex molecules which constitute the chief negative ions of the intracellular space. It is vital in the process of phosphorylation in the various phases of carbohydrate metabolism to form high energy bonds, and the subsequent release of this energy when these bonds are split. The same holds true in the formation of phosphocreatine and its breakdown.

Organic phosphorus is found in the phospholipids as lecithins and cephalins, and in nucleic acid, nucleotides, nucleoproteins and in phosphoproteins as casein. It is present in enzyme systems containing adenosine triphosphate and diphosphate, which with phosphocreatine pro-

vide the main sources of fast-acting readily available energy.

The blood inorganic phosphorus exists almost entirely in the plasma fraction; in infancy the concentration is about 5-6.5 mg. % and it gradually diminishes to the adult level of 3-4.5 mg. % (1.3-1.6 mM/litre, with a valence of 1; or 2.5-3.1 mEq./l. expressed as $HPO_4^=/H_2PO_4^-$, the average valence being 1.8 at a pH of 7.4).

III. Absorption of Calcium

In food, calcium is found in inorganic and organic forms, and is readily assimilable in either state. However, it is probably absorbed only in the inorganic soluble forms as the acid phosphate, chloride, and the carbonate which is soluble in dilute acids. The site of absorption is the upper part of the small intestine, especially the duodenum. This would suggest a straight diffusion process, but it is not certain. The absorption of a given amount of calcium is affected by the D vitamins, the pH of the intestinal contents, and the particular foods ingested. Parathyroid hormone itself has not been shown to increase calcium absorption,[38] whereas œstrogen administration has.[62]

With normal gastric acidity, compounds of calcium with weak organic acids such as the gluconate and the lactate are converted to calcium chloride, and if retained in the stomach for a sufficient period of time, even the less soluble basic phosphates may go into solution. However, it should be pointed out that the solution of calcium salts by gastric juice is not indispensable, as adequate absorption may occur in the presence of achlorhydria or after the administration of alkalinizing agents.

The duodenal pH is important and its normal range varies from 2.3 to 2.7. This determines whether most of the calcium is in the form of acid or basic phosphate. Since the former is more soluble, a higher acidity (a lower pH) favours absorption. Calcium chloride, calcium acid phosphate, and calcium carbonate are absorbed from the duodenum before the gastric acidity is neutralized and subsequent continued absorption is favoured by the fermentation of sugars to organic acids and by the digestion of proteins to produce amino acids. Aside from the relative acidity produced by amino acids, proteins per se seem to form soluble complexes with calcium.

A tendency towards decreased calcium absorption occurs when alkaline, high magnesium or potassium, or high phosphate foods are ingested. Such compounds tend to precipitate soluble absorbable forms of calcium to insoluble unabsorbable salts. Foods high in phytic acid, like whole wheat, are examples of high unabsorbable phosphate sources which tend to precipitate 6 atoms of calcium for every molecule of phytic acid. High oxalate foods such as spinach, potatoes, beans, endive, tomatoes, dried figs, plums, strawberries, rhubarb, cocoa, chocolate and tea, if taken in large quantities also tend to precipitate and so inhibit calcium absorption. Fats generally reduce calcium absorption even when the patient is on a high calcium and low phosphorus intake, because of the formation of insoluble calcium soaps. However, for some obscure reason, perhaps because of the production of soluble complexes with fatty acids, such fats increase the absorption of calcium if the diet has a low Ca/P ratio.

Little need be said of the decreased absorption which follows a protracted bout of diarrhœa, or is from a gastrocolic fistula, allowing the rapid passage of the intestinal contents through the bowel.

IV. Excretion of Calcium

Calcium is said to be excreted by the liver, kidneys and the epithelium of the large bowel. McCance and Widdowson[39] state, however, that little or no calcium is eliminated through the colonic wall. Its excretion via the various routes continues even upon a calcium-free diet or during a fast. Under these circumstances, it is obvious that the body is in a state of negative calcium balance.

On an ordinary mixed diet, 0.4-0.8 gram is lost in the fæces and about 150 mg. in the urine in a 24-hour period. Most of the calcium in the stool is derived from the unabsorbable food calcium. Only a small part is due to endogenous loss. The stool calcium rises with steatorrhœa, vitamin D deficiency, high P/Ca diets, in diarrhœa and so on.

It may be concluded from what has just been said that an increase or decrease in calcium absorption reflects itself in parallel changes in the urinary excretion. Thus the urinary calcium provides us with a convenient index of calcium absorption if no metabolic disease process is present.

The kidney threshold for calcium is about 6.5-8.5 mg. % of plasma. It rises with renal impairment provided no upset in the acid-base balance develops (the urinary calcium constituting a steadily diminishing fraction of the total calcium excretion). The urinary calcium excretion also decreases in hypothyroidism, hypopituitarism, hypoadrenalism and hypoparathyroidism, and with vitamin D deficiency.

A hypercalcinuria develops after the administration of parathyroid hormone, thyroxin, or glucocorticoids; if 20,000 or more units of vitamin D are given, or with AT-10; and in immobilization, whatever the cause.[40-46]

An increased bone reabsorption, either absolute or relative to a decreased bone formation, will also raise the urinary calcium excretion. This is seen in prolonged acidosis, whether it be metabolic, respiratory, or renal as in renal rickets, renal acidosis with osteomalacia or in the Fanconi syndrome; in patients with a ten-

dency towards a negative nitrogen balance as in osteoporosis, hyperthyroidism, Cushing's disease or syndrome, in severe cases of œstrogen or androgen deficiencies; in diseases affecting bone, as is occasionally seen in Paget's, multiple myeloma, bone metastases, xanthomatoses and sarcoidosis; and in primary and secondary hyperparathyroidism.

In renal disease with glomerular and/or tubular dysfunction, there is a poor conservation of base and the urinary calcium rises per se. Later on, bone resorption because of an ensuing acidosis results in an even higher urinary calcium excretion. This occurs in renal rickets with osteitis fibrosa cystica and in renal acidosis with osteomalacia.[38]

Not fully understood are the cases of idiopathic hypercalcinuria with normal plasma calcium levels. A lowered renal threshold seems to be at fault and infection has been incriminated as a cause.

V. Absorption of Phosphorus

In contradistinction to calcium, phosphorus is absorbed later and lower down the gastrointestinal tract. This is reasonable since the organic phosphate esters must be split by the action of the pancreatic and intestinal juices. It is probable that the sodium, potassium, and calcium acid salts are absorbed as such by a process of diffusion. The role of phosphorylation in the process of phosphorus absorption has not been fully elucidated. Vitamin D favours the absorption of calcium and there will be less of this element left for precipitation with phosphorus. As a result, vitamin D may be said to indirectly enhance absorption in the gastrointestinal tract.

Phosphorus absorption is decreased by the ingestion of a diet with a high Ca/P ratio, the relative excess of calcium tending to precipitate phosphorus. The administration of cations such as beryllium, strontium, magnesium, barium, thallium and aluminium, causes formation of insoluble unabsorbable salts with phosphorus. A deficient vitamin D intake will indirectly lower phosphorus absorption.

It is obvious that in colitis, and in diarrhœa from other causes where the intestinal contents move too quickly, a reduced phosphorus absorption will occur.

VI. Excretion of Phosphorus

Phosphorus is eliminated via the bowels and the kidneys. If the diet is a balanced one, the urinary phosphorus is about 55% of the total excretion. If calcium intake drops and if phosphorus intake is constant, the amount of phosphorus absorbed will rise and the proportion of the intake excreted in the urine will also increase. Therefore if the phosphorus intake is low, 70% of it is excreted via the urine, and if a low calcium/high phosphorus diet is given, 80% of the phosphorus appears in the urine. The proportion excreted in the fæces will increase when a diet contains much calcium or has factors which tend to inhibit phosphorus absorption.

The urinary phosphorus (about 1 gram/24 hours) is derived from the plasma inorganic phosphorus and from the splitting off of this element from its organic esters by the enzyme alkaline phosphatase. The renal threshold of this element is 2-3 mg. per 100 c.c. of plasma, excretion falling to a minimum at concentrations below this level.

With renal functional impairment, as in glomerulonephritis, the urinary phosphorus decreases and the fæcal phosphorus correspondingly rises. The urinary phosphorus increases with the administration of parathyroid hormone,[47] thyroxin, glucocorticoids, acids or acid-forming foods, AT-10, and with large doses of vitamin D. Actually, evidence suggests[48] that while vitamin D acts directly on the renal tubules to decrease the reabsorption of phosphorus, it may act indirectly by inhibiting the parathyroid glands, and cause an increased urinary reabsorption. One effect in a given individual may predominate over the other, or they may balance each other.

VII. Dietary Sources of Calcium and Phosphorus and Their Recommended Daily Allowances

Calcium is present in all natural foods. The largest sources are milk and its products, one imperial pint providing 0.8 g. (milk contains 0.12% calcium). The drinking of hard water can be an even greater source of calcium and provide up to 0.2 g. per day. Leafy vegetables such as spinach and rhubarb which contain oxalic acid will reduce calcium absorption considerably.

Phosphorus is present in all natural foods, chiefly in milk and its products, meat, liver, egg yolk, cereals, nuts and leguminous vegetables. Diets high in meat and milk will provide an adequate phosphorus intake.

Cereals such as wheat and oatmeal, owing to their high content of phytic acid, reduce absorption of calcium and other minerals found in the gastrointestinal tract. It should be emphasized that the six atoms of phosphorus in phytic acid are unavailable, and they readily combine with calcium to form insoluble salts. This explains the decalcifying action of certain cereals.

It is felt that on the average the calcium intake in growing children should be about 1 g. (40 mg./kg. of body weight) per day and during adolescence about 1.4 g. (60 mg./kg. of body weight). Men and women generally require about 0.8 g. (10 mg./kg. of body weight). However, during the latter half of pregnancy the

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intake should be raised to 1.5 g. and during lactation to about 2 g. As previously stated, 60% of the fetal skeleton is formed in the last two months of pregnancy, and over 80 g. of calcium may be lost during a normal lactation period. The phosphorus intake should be about 1.3 g. a day.

VIII. Action of the Natural "D" Vitamins

The chief function of the natural D vitamins (D_2 and D_3) appears to be that of directly promoting the absorption of calcium from the gut and indirectly of phosphorus. They also seem to facilitate the deposition of calcium and phosphorus in the bones at the epiphysial zone of provisional calcification. Whether this latter effect is due to a direct action on bone or whether it is due to a rise in plasma calcium and phosphorus levels consequent on increased absorption is not clear. Carlsson *et al.*[49] have shown another direct effect of the vitamin on calcium metabolism in bone. Using Ca^{45} they were able to demonstrate in rats that vitamin D causes an increased resorption of calcium and phosphorus from bone. Albright[38] maintained that the increased removal of bone salt observed after toxic doses of vitamin D was due to an increased urinary excretion of phosphorus with a resultant fall in the plasma phosphorus level. In Carlsson's experiments this possibility seemed to be excluded, since the serum phosphorus level was unaffected by the vitamin.

Vitamin D has also been shown to increase the urinary calcium excretion, and indeed Eager Howard has reported on cases of hypoparathyroidism treated with vitamin D_2 (calciferol) in which hypercalcinuria developed when a hypocalcæmia co-existed.[50]

As regards phosphorus metabolism, the administration of vitamin D to dogs seems to increase the maximal rate of reabsorption of phosphate in the renal tubules.[48] However, one is not sure whether this is a direct effect, or is secondary to a depressant effect of the vitamin on the parathyroid gland. Some evidence suggests that the direct renal effect may be increased phosphate excretion.[38, 51]

The net effect of vitamin D on phosphate excretion seems to depend on which of these two factors predominates and on the amount of calcium and phosphorus present in the diet and absorbed from the gut, at any given time. In fact, it is possible that all these factors may cancel each other out and cause no change in the urinary phosphorus excretion. This seems to have occurred in Carlsson's work.

The possible antagonistic action of cortisone and indirectly of ACTH to vitamin D will be subsequently discussed.

IX. Action of AT-10

This synthetic vitamin D (a photochemical derivative of ergosterol) seems to have a position intermediate between the actions of the natural D vitamins and parathyroid hormone.[38] Its action to increase calcium absorption from the gut is greater than the parathyroid hormone effect (which is almost nil), but less than that of D vitamins. Its action to cause an increased urinary phosphate excretion is considerably greater than that of D vitamins but it is not quite as effective as parathyroid hormone. Apart from its great expense and the need for caution in its administration (to prevent a marked hypercalcæmia), it may be used as a substitute for parathyroid hormone. Once a decision to use it has been made, one must not be guided by its price in the dosage to be employed, if failures in therapy are to be avoided.

X. Action of Parathyroid Hormone

Parathyroid hormone has an action qualitatively similar to that of D vitamins, but its action in enhancing calcium absorption is very slight. Its main effect according to the Albright school seems to be that of increasing urinary phosphate excretion, and so the plasma phosphorus level drops. This leads to a relative unsaturation of the plasma with regard to the calcium and phosphorus product, and calcium and phosphorus are mobilized from the bones. In this way, an attempt is made to restore plasma phosphorus to normal levels. An associated plasma calcium elevation occurs with a subsequent hypercalcinuria.

On the administration of parathyroid hormone or in hyperparathyroidism the plasma calcium rise is marked and one wonders whether the primary effect of the hormone is really on urinary phosphorus excretion. Collip *et al.*[52] in 1934 from their experimental observations on nephrectomized animals concluded that the primary effect of parathyroid hormone was to directly increase bone reabsorption. This theory seemed to be confirmed by the subsequent work of Ellsworth and Futcher[53] in 1935 and of McJunkin, Tweedy and McNamara[54] in 1937, and Stoerk.[55] They nephrectomized dogs and produced lesions identical with osteitis fibrosa cystica. However, they were criticized because no attempt was made to control the development of either acidosis after nephrectomy or the acidity of parathyroid hormone itself, nor did they do adequate nephrectomized animal controls. In 1943, Ingalls, Donaldson and Albright[56] undertook work on nephrectomized animals, this time controlling the pH, and they were forced to conclude that parathyroid hormone did have a considerable direct effect on bone, causing its increased resorption. However, they still felt that the primary action was on phosphate excretion.

Hence the two schools have concluded that the hormone has both actions—the Collip school, however, still insisting that the primary site is in bone. Grollman[57] in 1954 working with nephrectomized dogs has re-confirmed the direct action of parathyroid hormone in causing increased bone reabsorption.

As a result of the raised plasma calcium and the increased urinary calcium and phosphorus excretion, nephrolithiasis and nephrocalcinosis are prone to occur. The serum alkaline phosphatase level may be normal or raised. If raised, it suggests an attempt to increase new bone formation in order to try to keep in step with bone destruction.

With a decreased parathyroid hormone production, the tubular reabsorption of phosphorus is increased, bone resorption is diminished, and the plasma level rises. This results in a drop in the total and ionized plasma calcium. If the drop is sufficient, tetany may set in.[58]

XI. ACTION OF OTHER HORMONES

The exact mechanism of action of steroids on calcium and phosphorus metabolism has not been fully elucidated. *Œstrogens* seem to have a greater calcium retaining effect than *androgens,* and the opposite is true in relation to the nitrogen effect.[59] One may theorize that a drug which produced a positive nitrogen balance might also form more osteoid and therefore grab more calcium for bone formation. Experimentally it has been shown that androgens and œstrogens do result in increased osteoid bone formation.[60, 61] However, it is not known why œstrogens seem to have a greater calcium storing effect than androgens, especially when androgens exert a more potent nitrogen retaining power. Armstrong reported at the Macy Conference that œstrogens stimulated increased osteoblastic activity and that this was associated with a decreased osteoclastic activity and in many cases it was difficult to see any osteoclasts. When androgens were superimposed upon œstrogen therapy, there was no increase in the above activities. Hence it may be prematurely concluded that œstrogens either decrease bone reabsorption (unlikely in the light of Govaerts'[62] work) as well as stimulate new bone formation, or that they may have a stronger tendency to convert stored protein into osteoid than androgens. This does not rule out a possible specific direct action of œstrogens, or for that matter of androgens, on calcium metabolism in its retention by renal tubular cells. Govaerts, Dallemagne and Melon,[62] using radioactive Ca^{45} and α-œstradiol, have found that œstrogen produces in animals an increase in the calcium turnover of old bone tissue, increases calcium retention in bones and tissues, and decreases urinary excretion. Calcium absorption from the gastrointestinal tract was also increased under the influence of this œstrogen.

The *adrenal steroids* (especially the glucocorticoids), with their anti-anabolic and/or catabolic action on proteins, tend to decrease bone matrix formation and perhaps even increase bone resorption, the net result being a strong tendency toward a negative nitrogen and calcium balance.

Anderson *et al.*[63] reported on the increased fæcal calcium excretion in patients with Boeck's sarcoid who had a hypercalcæmia which returned to normal levels on cortisone therapy. Increased requirements for vitamin D were found by Moehlig and Steinbach[64] in hypoparathyroid patients who were adequately treated with vitamin D and then developed tetany when cortisone was administered for an ensuing coincidental multiple osteoarthritis. They also reported the development of tetany in a patient with sprue given cortisone therapy. Hopkins, Connor and Howard[65] observed the return to normal levels of elevated plasma calcium when three patients with sarcoid, three with multiple myeloma, one with reticulum cell sarcoma, one with chronic lymphoid leukæmia and one with "questionable atypical Cushing's syndrome" were all treated with ACTH. No change in the ratio between ultrafiltrable calcium and total serum calcium was noted by the latter investigators. They offered no explanation of the return to normocalcæmic levels. It is suggested that a process of competitive inhibition may exist between vitamin D and cortisone.

In as yet unpublished work of our own, careful metabolic balance studies were carried out on two paraplegic patients with the usual hypercalcinurias. When they received 150 mg. of cortisone per day, both showed a drop of about 20% in the urinary excretion of phosphorus. One of these patients had a concomitant rise of 25% in fæcal calcium excretion, the other a 4% drop. In both cases no significant alteration in the urinary calcium excretion was noted. The results on nitrogen balance were equivocal.

Becks *et al.*,[66, 67] and later Baker and Ingle,[68] showed that ACTH causes a retardation of chondrogenesis and osteogenesis in the tibiæ of immature and adult rats. Growth hormone acted antagonistically to ACTH. Ulrich *et al.*[69] studied the effects of ACTH on radioactive Ca^{45} in intact and hypophysectomized male rats. They concluded that ACTH did not appear to affect the uptake of Ca^{45} by the femora of the intact animals but did significantly reduce the uptake in the hypophysectomized group. The urinary excretion of radio-calcium did not significantly increase in the controls or in the hypophysectomized animals.

Thyroxin, because of rapid protein turnover, produces an increased urinary calcium and phosphorus excretion and tends to shift the patient into negative balance. Its action may be as with glucocorticoids, and/or a direct renal tubular effect. No evidence as yet exists for the latter point of view.

XII. ROLE OF THE KIDNEY IN CALCIUM AND PHOSPHORUS METABOLISM

The urinary phosphorus concentration is greater than that of calcium, hence renal impairment results in a greater phosphorus retention than calcium. We have already discussed the renal threshold for these two elements and the action of the D vitamins and hormones.

In uræmia, urinary phosphorus excretion decreases, so that the plasma phosphorus level rises and consequently the ionized calcium level falls. If the hypocalcæmia is sufficient, twitchings (tetany) and convulsions with death may occur. Intravenous administration of magnesium will lower the ionized calcium even more, adding insult to injury.[23] If the uræmic condition persists for a sufficient length of time, a secondary hyperparathyroidism will develop, with osteitis fibrosa cystica, acidosis and occasionally nephrolithiasis or nephrocalcinosis as sequelæ.

XIII. BODY PHOSPHATASE

Phosphatases[58, 70, 71] are enzymes which hydrolyze organic phosphate esters, with liberation of free inorganic phosphate. In the case of bone, alkaline phosphatase releases a local excess of phosphate with an increased tendency to precipitation on bone matrix. Newer concepts on this theme have been mentioned.

In the fetus and in growth, the largest concentrations of phosphatases are found in forming or growing bones and teeth. In adults the intestinal mucosa contains the largest amounts per unit of wet weight, followed by adrenal cortex and bone.

There are many types of phosphatases[72] but only three seem to be biologically important. They are: (1) alkaline phosphatase (with an optimal activity at pH 9-9.6), found in plasma, bone, kidney, intestine, mammary gland, spleen, lung and white blood cells; (2) acid phosphatase (active maximally at pH 6), found in erythrocytes and yeast; (3) acid phosphatase (with a maximal activity at pH 5), found in prostatic epithelium, spleen, kidney, blood plasma, liver and pancreas. The phosphatases are activated by magnesium, iron, manganese, cobalt, nickel, vitamin C, and glycine. They are inhibited by copper, zinc, and cholic acid.

Bone remains the chief source of plasma alkaline phosphatase even when all the abdominal viscera are removed. Normal liver function may have a slight effect on the plasma level.

Not often realized is the fact that plasma normally contains less than 3 units of acid phosphatase per 100 c.c.[73-75] Since children and women have similar plasma levels,[73] the prostate cannot be the main source. The enzyme seems to be derived from such organs as the liver, spleen, bone, and kidneys, as well as from the prostate.

As the red blood cells have a fairly high acid phosphatase concentration, it is important not to lyze these cells when testing for this particular enzyme.

According to Bodansky[76] a unit of alkaline phosphatase activity is "equivalent to the actual or calculated liberation of 1 mg. of phosphorus as the phosphate ion during the first hour of incubation at 37° C. and pH 8.6 with the substrate containing sodium beta-glycerophosphate, hydrolysis not exceeding 10% of the substrate". Normal values in children are 5-14 Bodansky units, 15-20 King-Armstrong units, and 0.17-0.34 Kay units. In adults the normal values are 1.5-4.0 Bodansky units per 100 c.c., 3.7-13.1 King-Armstrong units, 0.1-0.2 Kay units and 2-8.6 Shinowara units.

Alkaline phosphatase is partly excreted by bile and partly by the kidneys. Biliary retention is only one of the factors responsible for the marked increase in the plasma alkaline phosphatase. Here the rise is due to obstruction of the biliary ducts in part or toto, or smaller rises may be associated with hepatocellular disease.

Increases of a moderate to a marked degree in the serum alkaline phosphatase activity are generally observed in those disorders associated with an increased osteoblastic activity. Lesions associated with an increased osteoclastic activity are much less apt to be accompanied by a significant rise. Thus in hyperparathyroidism the serum alkaline phosphatase activity may be normal or only moderately elevated.

Increased plasma or serum alkaline phosphatase activity[77] has been seen in active rickets (20-190 units) and in the polyostotic form of Paget's disease (15-125 units, or up to 25 units if only one or two bones are affected). A moderate increase may be seen in clinical and experimental hyperparathyroidism (20-40 units). Slight elevations of 5-15 Bodansky units, although rare, have been reported in generalized osteoporosis, in marked hyperthyroidism, in metastatic carcinoma affecting bone, in osteogenic sarcoma, in Hodgkin's disease, in lymphosarcoma and leukæmia affecting bone, in polyostotic fibrous dysplasia, in healing fractures, in Gaucher's disease with bone resorption, in osteosclerosis fragilitas generalisata (marble bone disease), in renal rickets (rickets being a misnomer) and in multiple myeloma.

As previously mentioned, in hepatocellular disease or in biliary obstruction the value may rise to 60 Bodansky units. In patients with intra-abdominal malignancy of various types, a significant rise in the plasma alkaline phosphatase in the absence of skeletal metastases suggests metastases in the liver.

For completeness it should be stated that an increase in alkaline phosphatase activity may be found during periods of calcification of hæmorrhages as in scurvy, in active tuberculosis and Boeck's sarcoid, in chronic myeloid leukæmia, in tumour cells, in heterotopic bone, in muscle and fibrous tissue in the pre-ossification

stages of myositis ossificans, and in the liver, spleen and kidneys in myelogenous leukæmia.

The part played by alkaline phosphatase in forming fibrous protein, in rendering osteoid material calcifiable, in catalyzing the further breakdown of beta-glycerophosphate in glycolysis and in enhancing transphosphorylation processes has already been dealt with.

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RUPTURED SPLEEN

In a review of 17 cases of ruptured spleen, with one death, Tagart (*Brit. J. Surg.*, 43: 283, 1955) noted that the injury was sometimes surprisingly slight, especially in children. The spleen was the organ most commonly injured in non-penetrating abdominal trauma, and the only other organ damaged was the left kidney. The most valuable single sign of splenic rupture is pain in the left shoulder. Plain radiographs of the abdomen often showed depression of the left colic flexure and medial displacement of the fundus of the stomach.

Splenectomy is the proper treatment, and an upper midline incision with occasionally a transverse extension to the left is recommended. In one case a left subphrenic abscess resulted from damage to the greater curvature of the stomach at operation.

No impairment of general health was found in the follow-up but one-third of the patients had a slight polymorphonuclear leukocytosis.

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PRENATAL SEX DETERMINATION

Would expectant parents benefit from knowing the sex of their unborn child? This is a question on which there will be divided opinion, or no opinion at all in the absence of experience. If a suitable test of prenatal sex becomes available, it will no doubt be requested frequently to satisfy parental curiosity, and society will probably adjust to this development with ultimate benefit as it has done following other advances in biological science. There is no strictly medical advantage in knowing fetal sex. A test of prenatal sex is permissible, therefore, only if any specimen required for the test can be obtained by a simple and perfectly harmless procedure. A reliable method has been described recently, but it is impractical because a sample of amniotic fluid must be taken to obtain cells of fetal origin. This new development is of interest nonetheless, since it may point the way to a perfectly safe procedure through research paths that are not now apparent, and since the demonstration of a sex difference in the structure of cell nuclei in the human fetus will likely encourage further studies on the cells and tissues of human embryos. The development of a cytological test of fetal sex came about in the following manner.

Rosa and Fanard[1] showed in 1949 that the cells obtained from a centrifuged sample of amniotic fluid differ, depending on whether the fetus is male or female. The cells are mainly acidophilic in the presence of a male fetus, and come from the digestive and respiratory tracts or from the surface of the fetus and its membranes. When the fetus is a female there is a high proportion of basophilic cells from the mucosa of the fetal vagina. This test is reliable only in the later stages of pregnancy when maturation of the reproductive tract is well advanced.

The procedure of Rosa and Fanard has been refined and made applicable in theory, but not in practice, to earlier stages of pregnancy by taking advantage of the distinctive morphology of cell nuclei according to sex. Female nuclei contain a mass of sex chromatin derived from the XX-sex chromosome complex, while male nuclei with their XY-sex chromosomes lack the sex chromatin.[2] The study of cell nuclei from this point of view and its valuable applications to clinical problems have been well reviewed recently by Lennox.[3] With this background, cell nuclei in smears from centrifuged human amniotic fluid were examined for the presence or absence of sex chromatin by Serr *et al.*,[4] James,[5] Fuchs and Riis,[6] Makowski *et al.*,[7] Sachs *et al.*,[8] Shettles,[9] and Dewhurst.[10] All of these authors agree that with appropriate care in the preparation and study of the smears the sex of the fetus can be determined without error. However, they wisely refrain from recommending use of the test, and Dewhurst definitely warns against it, since the information so obtained lacks any medical value that would justify aspiration of amniotic fluid. This sensible attitude will receive strong support from the medical profession generally.

Fuchs and Riis, and Sachs *et al.*, suggest that their test of prenatal sex may have some value in veterinary practice. Aside from the complication of multiple births in many animals, the method is applicable only when the chromatin pattern of the nuclei is such that the presence or absence of sex chromatin can be established clearly. This varies from one species to another. In cattle, nuclei generally are unsuitable for chromosomal sex determination because there are numerous large chromatin clumps that obscure the sex chromatin, although the chromosomal sex is clear in the large nuclei of nerve cells.[11] Cells of the bovine fetus have not been studied, but it seems unlikely that they will be suitable for detection of chromosomal sex. Some other domestic animals may fall into the same category.

This newest development in nuclear cytology cannot be put into medical practice for prenatal sex determination because there are sound reasons for objecting to uterine puncture for

the sole purpose of satisfying the curiosity of prospective parents. Nevertheless, the work will serve as a stimulus to further research and we may confidently expect to hear of further developments along these lines.

M. L. BARR

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Editorial Comments

SPLENECTOMY AND BLOOD DISORDERS

Whether or not the spleen should be removed from any particular patient suffering from a blood dyscrasia depends in part upon contemporary views as to the physiological and pathological roles of the organ and in part upon accumulated experience of the results of splenectomy in the type of case under consideration. As both of these criteria have undergone change in recent years, a brief glimpse at the present picture might prove of interest.

Hayhoe and Whitby[1] review the normal functions of the spleen. They point out that reservoir action does not seem to be of significance in man and that healthy red cells exposed to stasis within the sinusoids have not clearly been shown to suffer damage. There is much evidence to suggest that a humoral agent originates in the spleen which influences the maturation of blood cell precursors of all types and also the release of mature forms to the periphery. Undoubtedly the abundant lymphoid tissue of the spleen renders the organ a major site of antibody production and equally certain is the importance of the reticulo-endothelial elements in their function as scavengers.

Hæmopoietic activity in the spleen is confined normally to the second to fifth months of intrauterine life, but pathological processes, especially those such as myelofibrosis, which virtually obliterate the marrow, may result in reversion by the spleen to its early function of providing blood.

Under abnormal circumstances, normal functions of the spleen may contribute materially to the over-all clinico-pathological picture. Should, for example, the red cells in circulation be defective, they may undergo rapid destruction in the spleen. This may be due in part to an increased sensitivity to the action of lysolecithin in the sinusoids and in part to an inherent liability to phagocytosis which might, in turn, be further aggravated by the effects of lysolecithin. Thus the spherocytes of hereditary hæmolytic anæmia (familial acholuric jaundice) have but a limited life span in the body, and splenectomy almost always gives marked and lasting benefit (Dacie[2]).

So also Smith *et al.*[3] found splenectomy to give relief in Cooley's anæmia in which there is an inherited defect of the red cells associated with the presence of an abnormal hæmoglobin. No longer to be restricted by the epithet "Mediterranean anæmia", this entity is being diagnosed more and more frequently in North America because refractory hypochromic anæmias more commonly are being subjected to electrophoretic investigation. Glenn *et al.*[4] consider the indications for splenectomy in this condition to be either a spleen large enough to cause disability through sheer size or else a progressive increase in the rate of hæmolysis as judged by shortening of the intervals between transfusions.

Thus we approach more controversial topics. Acquired hæmolytic anæmia may be idiopathic (that is, without discernible cause) or may be associated with and symptomatic of an underlying process such as a leukæmia. In the symptomatic group splenectomy is seldom considered because of the nature of the primary disease; however, should hæmolysis dominate the picture, the operation may provide a valuable palliative measure in selected cases.

Hayhoe and Whitby consider that about half of the patients in the idiopathic group derive benefit from splenectomy. The mechanism of the hæmolytic process is not fully understood and may vary somewhat from case to case; the subject is fully discussed by Dacie.[5] Some patients respond well to the administration of cortisone or ACTH and some do not. Neither this nor any other feature, clinical or hæmatological, will serve as a guide to the likely effects of removal of the spleen, which operation must therefore be considered largely as a gamble in any given case. The natural course of the disease usually being progressive, there is, however, less hesitation to advocate surgery than a decade ago when splenectomy was considered to offer no likelihood of relief in idiopathic hæmolytic anæmias associated with a positive antiglobulin reaction.

Contemporary thought concerning idiopathic thrombocytopenic purpura tends to a comparison with acquired hæmolytic anæmia (Harrington[6]). Platelet antibodies sometimes may be

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demonstrable, but not in all cases. However, plasma from a patient with idiopathic thrombocytopenic purpura, when injected into a normal subject, apparently may cause not only lysis of existing platelets but also interference with the production of new platelets by megakaryocytes (Stefanini[7]). While interval splenectomy is commonly practised in the chronic, relapsing form of the disease, usually providing a clinical "cure", recurrence of bleeding a few or many years subsequently may cause disappointment, and not all of these cases are associated with the presence of accessory spleens.

In the acute form of idiopathic thrombocytopenic purpura, seen particularly in children and often following a fever or the administration of a wide variety of medicaments, spontaneous remission is the rule within a matter of a few or several weeks. Transfusions may be required if blood loss is material. Cortisone, ACTH or, as Dameshek[8] prefers, prednisone may control purpura without obvious effect either on the platelet count or on platelet antibody titre if such is demonstrable. Splenectomy is called for only if hæmorrhages are profuse and widespread (cerebral extravasations always being feared) or if manifestations persist longer, let us say, than three months. It is for surgery under such conditions that platelet transfusions are likely to prove of most value, although blood loss is often surprisingly small with no special precautions other than careful operative technique. To effect a transfer of platelets, fresh blood collected in siliconed bottles, or perhaps better in plastic packs, must be used. From this material may be prepared concentrated suspensions of platelets.

In idiopathic thrombocytopenic purpura the bone marrow usually shows an increase in megakaryocytes without evidence of platelet formation. In another group of patients anæmia, neutropenia and thrombocytopenia, individually or in combination, may be present with enlargement of the spleen, a marrow biopsy showing increased cellularity and a picture of "maturation arrest" in the precursor cells. This constitutes Dameshek's concept of "hypersplenism" and there are obvious parallels with idiopathic thrombocytopenic purpura. As hypersplenism—presuming that this is acceptable as an entity—may be idiopathic or may accompany splenomegaly from many different causes (e.g. Banti's syndrome; the reticuloses), comparison may also be made with the acquired hæmolytic anæmias.

The primary form of hypersplenism usually responds well to splenectomy, but surgery in the secondary or symptomatic cases must obviously be reserved for instances in which the underlying lesion is very chronic. Again one can see a parallel with acquired hæmolytic anæmia; Hunter and Kiernan[9] describe cases of the latter associated with, for example, a chronic leukæmia, in which the hæmolytic process dominated the clinical picture and in which benefit resulted from splenectomy. An extreme example is quoted by Edwards,[10] who refers to a case of myelosclerosis with marked evidence of a hæmolytic process and in which splenectomy, performed contrary to all previous conventions, produced amelioration.

It is patent that decision whether or not to remove the spleen in any given case of a blood disorder must depend upon full investigation, leading to as precise a concept as possible of the mechanism involved, and that the surgeon must lean heavily upon the opinion of a clinical hæmatologist. Surprising results will continue to occur as long as our knowledge of so many of the dyscrasias under consideration remains so limited. An experience of Edwards is monitory; he observed a "cure" by splenectomy of a patient stated to have true aplastic anæmia, a condition usually adjudged hopeless apart from the tenuous existence of a "transfusion life". It seems to be the case that if, after full enquiry and debate, doubt remains as to the likelihood of benefit from splenectomy in any patient with a blood disorder of the type we have been discussing, then the tendency is to resort to surgery. Barring the operative risk, harm to the patient is unlikely and benefit always possible.

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THE EFFECTS OF POSTURE ON KIDNEY FUNCTION

It is well known that changes in the rate of urinary excretion will result from changes in posture; the increased output in the recumbent position was at first attributed to the increased blood flow through the kidney. It became evident however that the mechanism is more complicated than this, and recent papers on the subject[1, 2] give a glimpse of the extent of these complications. The investigations described were made under rather abnormal conditions of induced diuresis by high water loading or by infusion with sodium sulphate solution. It would appear however that the altered rate of urinary

flow does not depend solely on the glomerular filtration rate, although this was found to be slightly decreased on standing. There are alterations also in the ability of the proximal and distal tubular epithelium to reabsorb certain ions. A marked and immediate decrease in sodium excretion was found to accompany the antidiuretic effect of standing, and Surtshin and White[1] claim that this is due to an increased reabsorption of sodium in the proximal convoluted tubules. Epstein *et al.*[2] confirm the fact of this renal sodium retention and find also that, in their sulphate-infused subjects, there is little change in the urinary flow and an increased excretion of potassium and hydrogen ions. The latter changes had not been noted by other workers using different methods of inducing diuresis[3, 4] and the present authors conclude that the process was unmasked by the presence in the glomerular filtrate of large numbers of negatively charged and unabsorbable sulphate ions. They put forward the theory that, in the experimental circumstances, sodium is retained in standing subjects as a result of active ionic exchange, across the tubular epithelium, for both potassium and hydrogen ions. The significance of such findings, or why renal tubular activity should be altered by posture, is still far from clear and is perhaps wisely not discussed by the authors. The problem at present still revolves around the further elucidation of exactly what changes occur and where.

ROSEMARY LINDAN

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MULTIPHASIC SCREENING

Mass screening procedures have been widely used in the past for such conditions as syphilis and pulmonary tuberculosis. More recently the employment of a battery of tests has been used in order to detect asymptomatic disease. Only patients with positive or equivocal findings are ultimately referred to a clinician. This multiphasic screening technique has several obvious advantages. Since the tests are conducted by technicians, the physician's time is conserved, the cost of the survey on a per capita basis is low, and in addition it has a definite health education value. Furthermore, it has been demonstrated that a significant degree of latent or unsuspected disease is brought to light—in many cases, in the early stages of the condition.

An evaluation of various laboratory procedures employed during an annual physical examination of a group of 500 executives has been published by R. J. Bolt *et al.*[1] In this group one-half were found to have one or more defects requiring treatment, of which 70% were not known to exist before the examination. Of all defects 12.3% were discovered solely by the aid of the laboratory, and in the remainder laboratory studies played an essential part in confirming the clinical diagnosis. The tests used routinely consisted of blood count, sedimentation rate determination, urinalysis, blood serology, stool examination for occult blood, and fasting blood sugar, non-protein nitrogen and acid and alkaline phosphatase determinations. Annual radiological investigations included studies of the chest and upper gastrointestinal tract, and cholecystograms with biannual colon x-ray. Electrocardiography and sigmoidoscopy were also performed annually.

The authors have found routine use of acid and alkaline phosphatase tests and the occult blood stool test to be of little value. The non-protein nitrogen blood level estimation was useful only in cases where renal dysfunction had already been established clinically. As was to be expected, routine x-ray studies detected many abnormalities previously unsuspected. Sigmoidoscopy is recommended as a worth-while procedure; single or multiple polyps were discovered in 9.6% of patients and sigmoid carcinoma was observed in one instance. The electrocardiographic findings were somewhat disappointing and the finding of abnormalities on routine tracings was by no means diagnostic. However, as the authors have indicated, it will require surveillance for 10 years before final conclusions can be drawn as to their true significance.

In the early diagnosis of chronic and neoplastic disease multiphasic screening has a definite part to play. With the continually widening public interest in the etiology of these conditions it is likely that more multiple screening programs will be operated in the future. However, there are certain shortcomings to this type of case-finding technique, especially in the interpretation of individual laboratory tests. If these limitations are borne in mind, there is no reason why incipient disease in large numbers of persons cannot be detected by this method. It should be stressed that the screening process does not replace comprehensive health medical examination but rather is supplementary to it.

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Medical News in brief

ARTERY REPLACEMENT WITH NYLON TUBES

Studies have been in progress for some time of materials which could be used for construction of prefabricated tubes to replace human arteries as grafts. Such a tube would have to be easily sutured and wrinkle- or kink-proof on flexion. Edwards and Tapp of Birmingham, Alabama *(Surg., Gynec. & Obst.,* 102: 443, 1956) report their experience in 14 cases in which they used 15 nylon grafts to replace portions of peripheral vessels. The tubes they used were flexible, braided nylon tubes, treated with acid, and available in various lengths and diameters. These tubes may be sterilized by autoclaving, are easy to manipulate and suture, and give a low incidence of thrombosis, even in small vessels. There is little blood loss through the tube after implantation, and the tube can be flexed to 180° without obstruction and therefore can be used in areas such as the groin or the popliteal space.

A UNITARY THEORY FOR LUNG CANCER, CORONARY THROMBOSIS AND LEUKÆMIA: A DEFICIENCY OF ESSENTIAL FATTY ACIDS

In a recent letter to the *Lancet* (1: 383, 1956) H. M. Sinclair of Oxford has advanced an important theory which links not only lung and stomach cancer but also coronary thrombosis, leukæmia, disseminated sclerosis and other conditions with a deficiency of the polyethenoid essential fatty acids which include arachidonic and linoleic acids. Linoleic acid needs vitamin B_6 for its conversion to arachidonic acid. These acids are contained in peanut, sunflower, wheat germ and other plant oils.

The thesis advanced is that the dietaries of the technologically more advanced peoples are becoming increasingly more deficient in the essential fatty acids and increasingly more rich in saturated fatty acids and unnatural acids which may act as antivitamins. This disastrous change arises partly from processes of manufacture such as hardening of fats and partly from the use of low-extraction flour "improved" with oxidizing agents. Since the requirements of males for essential fatty acids are much greater than of females, the consequences are more serious in males. If cholesterol becomes esterified with abnormal or unusually saturated fatty acids, these abnormal esters are less readily disposed of and so cause atheroma.

Phospholipids such as phosphatidyl ethanolamine contain abnormal phospholipids which increase blood coagulability contributing to thrombosis. Deficiency of normal phospholipids, or presence of abnormal phospholipids, may lead to seborrhœic eczema, peptic ulcer and also possibly disseminated sclerosis.

Deficiency of polyethenoid fatty acids may increase susceptibility to noxious agents including the carcinogenic effect of x-irradiation and chemical carcinogens. From this may result leukæmia and carcinoma of the bronchus and stomach in males.

A great deal of this theory is based on sound experimental evidence, and this letter should be carefully perused by all research workers in the various fields mentioned and especially by governmental agencies responsible for the pure foods laws. Perhaps our foods are becoming chemically too "pure" for our own good.

HYPOTHYROIDISM PRESENTING AS MENTAL DISORDER

In 1949 the London physician, Dr. Richard Asher, published an arresting paper entitled "Myxœdematous Madness", in which he drew attention to the common error of overlooking hypothyroidism in a case of mental disorder. Dr. Turmel and his colleagues from the Clinique Roy-Rousseau, Quebec, *(Laval méd.,* 21: 295, 1956) now emphasize again this common diagnostic error. Between 1945 and 1955 they had admitted to their clinic 24 women aged between 13 and 47 years, all of whom were suffering from mental disorders due to hypothyroidism which had not been diagnosed by the outside practitioner. In 15 cases the facies was diagnostic; in 11 cases the woman had a pale, pasty, waxy, bloated face. In four cases the skin was dry and coarse and in three cases the hair was falling out. Exophthalmos was noted three times, and four patients had œdema elsewhere than on the face. When interrogated, 11 complained of sensitiveness to cold, 12 had menstrual disturbances. Basal metabolism varied from —16% to —45%. Blood cholesterol level was a good diagnostic aid. All patients except one responded excellently to treatment with thyroid extract in a dose of 1-1.5 g. daily, rising to 3-4 g. daily. Improvement set in within 10 days.

PARIETAL PLEURECTOMY FOR RECURRENT SPONTANEOUS PNEUMOTHORAX

Spontaneous pneumothorax in apparently healthy people is relatively common and almost always due to rupture of a subpleural air vesicle. It is responsible among young men for one out of every thousand hospital admissions. It also has an annoying habit of returning; the recurrence rate has been reported as from 15% to 42% in large series. At an American Air Force base, recurring spontaneous pneumothorax was the second most common cause of admission to the thoracic surgery section *(Surg., Gynec. & Obst.,* 102: 293, 1956). A new technique was devised at this base for surgical treatment of the condition when local excision would have been inadequate, either because resection of all the blebs would entail too great a loss of lung tissue or because no lesions could be found on the surface. Parietal pleurectomy was used in these cases, being preferred to chemically or mechanically induced pleuritis because it carried fewer complications, shortened stay in hospital and eliminated the chance of recurrence. After nine total or subtotal pleurectomies, complications were negligible. There was no measurable loss of pulmonary function and patients quickly returned to full duty.

(Continued on advertising page 43)

PUBLIC RELATIONS FORUM

Conducted by L. W. HOLMES,
Assistant Secretary, C.M.A.

XVIII. BUILDING GOOD ATTENDANCE

NO PUBLIC RELATIONS PROGRAM, indeed no society-sponsored activity, can be pursued successfully without strong membership support and co-operation. In many societies these qualities are lacking; members are members only on the books. They do not attend meetings and are uninformed about society activities. The medical society can serve itself, its membership and these non-active physicians, and at the same time achieve excellent internal public relations, by stimulating improved attendance.

Few societies will dispute that there is a definite need for the improving of attendance at their meetings. But how will it be accomplished? There is no magic formula for guaranteed attendance. Nevertheless, there are several primary factors which contribute to good attendance. They are:

1. Outstanding scientific programs and timely, uncomplicated business meetings. Physicians will attend if there is sufficient interest in the meeting; otherwise they will not.
2. Food and fellowship.
3. Adequate notification of meeting. An effective plan is to send written notice to each member a week before the meeting date, and to make a follow-up telephone call the day before or the day of the meeting.
4. A central location within easy reach of members.
5. Personal initiative displayed by the officers of the society. Without personal interest of doctors in the duties of their elected offices, a society cannot hope for success.
6. Personal interest of each individual, and good relationships between doctors. Attendance in any organization that is not compulsory must come from the individual's desire to contribute to that group.

OUTSTANDING PROGRAMS

Good scientific programs and timely, uncomplicated business sessions probably represent the most important factor affecting attendance at meetings of the medical society.

Material included in the scientific program should be of general interest to the majority of the membership and should be presented with their problems in mind. The importance of securing prominent clinicians, preferably from out-of-town, should not be underestimated in planning a good scientific program. Some societies bring in outstanding guest speakers to present programs covering varied topics, and augment the material by excellent papers from local men. Members should also be given an opportunity to discuss the topic and problems related to it after each presentation.

In arranging programs, it is also important that officers of the medical society seek to prevent both business and scientific presentations from becoming too long or too involved. If the program lacks brevity and conciseness, attendance at future meetings is likely to suffer. The secretary of one medical society wrote on this point:

> An hour and a half is allocated for each meeting, including 45 minutes for the program and 45 minutes for business. We feel it is important that the doctors realize that only a specified amount of their time can be given at the meetings, and that they can budget their time accordingly.

FOOD AND FELLOWSHIP

The serving of food and the scheduling of a social hour frequently will contribute to good attendance. Many small societies always hold dinner meetings; the larger societies may find it difficult to serve large numbers and as a result do not plan dinner meetings frequently. Another approach is to serve refreshments after the meeting.

Some societies routinely schedule a social hour preceding the dinner.

The price of a dinner may also be used as an incentive to stimulate attendance. One society reports that at the start of the year each member is charged the price of a dinner for each meeting. This assessment is included in the annual dues of the society. Thus, if an individual does not attend a meeting, he forfeits the dinner for which he has already paid.

ADVANCE NOTICE

Physicians, because of their busy schedules and advance appointments, should be given adequate notice of the time, date and place of meeting. It is important, too, to include information on the scientific program and items on the agenda for the business session in the advance notice. Some doctors are more likely to attend if they know something about the program. This advance material will also give them an opportunity to participate actively in the meeting.

The usual method of notification is a postal card listing date, time and place of meeting and briefly outlining the program. In addition, some society secretaries will telephone each member to remind him of the meeting and to determine if he will attend.

A unique notification plan was devised by the president of the Travis County (Texas) Medical Society. He wrote personal letters to the 200-odd members of the society urging attendance at meetings throughout the year. He started out by saying he was out to get each member . . . to get them to attend meetings of the society. He

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pointed out that he was counting on their ideas, and would appreciate their active participation in the meetings. Shortly thereafter, he wrote a letter to the wife of each physician, asking her co-operation by hiding her husband's pipe and slippers on the third Tuesday of each month, and urging her not to schedule any social obligations on that evening. A third letter was then mailed to each doctor's secretary. The dates of all meetings of the county medical society were listed for the year, and the secretaries were asked to circle the dates on the calendar. The society president also suggested that secretaries remind the doctors on each scheduled meeting date of the medical society.

The foregoing points up the importance of holding meetings on specifically designated dates throughout the year, and over a period of years, if possible.

CONVENIENT LOCATION

Selection of a site or meeting place which is convenient to a majority of the membership is another factor which may encourage attendance. For most societies this is not a particularly vital factor. It may be, however, in large communities. It is suggested that meetings be held at a central location in the community.

WOMEN'S AUXILIARY

Where there is a Women's Auxiliary, concurrent meetings will assist attendance of both organizations. If dinner meetings are held, perhaps the wives can be invited to dine with their husbands, and then conduct separate meetings. Occasionally it may be possible for the two groups to hold a conjoint meeting at which mutually interesting subjects are discussed. These joint meetings can help strengthen the society's program, particularly its public relations program, stimulating the interest of wives in specific PR objectives which they might help pursue.

LEADERSHIP

A football team must have a quarterback to call the plays, and so must every organization have good leadership if it is to accomplish its objectives. The leadership and initiative of a society's officers can do much to stimulate attendance.

The story of how the initiative of a newly elected president transformed a society which previously met only once a year into an active organization is told by the secretary of another Texan medical society.

> Having been elected our president for the year, Dr. . . . . 's inaugural address was, in reality, a rousing pep-talk. In concluding his address, Dr. . . . . expressed chagrin at our total lack of interest in the stirring events of medical interest to our local state, and national medical societies; and actual embarrassment at having to admit he was a member—and the president—of such an unprogressive medical society.
>
> Dr. . . . . was well aware of the many discouraging attempts in the past to stimulate enough interest to break up the one-meeting-a-year habit that had become so firmly established. However, he decided to do something about it. So he instructed the secretary to arrange a series of informal meetings for the purpose of viewing and discussing selected medical moving pictures. The response was encouraging. Then the president gave an informal house party for the members and their wives.
>
> Warmed by this renewed feeling of fellowship, and with a returning pride in the revived activities of their society, the ensuing annual meeting of the members for 1954 was most enthusiastic and productive. Resolutions were adopted to resume regular meetings to be held the first Tuesday in each odd month of the year; to invite outstanding speakers for our scientific program with our neighboring county societies; and to arrange for convenient accommodations in the presence of adequate and excellent food.
>
> Meetings have followed with 100 per cent attendance; and the members have been rewarded by interesting and instructive talks by outstanding specialists from [principal cities in the state].
>
> Availing themselves of the opportunity these meetings afford, the members have not neglected important topics of interest to themselves and their community. These topics include gamma globulin, sanitation, and nurses' training. So our business meetings also are assuming added interest and greater scope.

THE INDIVIDUAL MEMBER

Outstanding programs, the serving of food, adequate notification of meetings, a central location, concurrent meetings of the Women's Auxiliary, and leadership and initiative displayed by the elected officers are important factors in stimulating attendance at meetings of medical societies. Yet, despite these factors, attendance rests solely with the individual. Each individual must decide whether he will or will not attend.

Interest of the individual is vitally important in any organization which does not *require* attendance. Attendance at medical society meetings, being non-compulsory, must come from the individual's desire to contribute to that organization and the sense of need created in the individual by the organization. Ultimately, it is the individual and all the forces which motivate him into action that makes or breaks a society.

Most doctors will be more inclined to attend meetings if they have a job to do, and if they feel they are vital members of the team. A physician who does not have an assignment, and who comes to meetings solely to listen rather than participate, is likely to lose interest. The job assigned to the member should be planned according to the individual's desires and abilities. These may be assessed by questionnaires in which he submits his areas of interest and those in which he would be willing to serve. Committee appointment, however, is not enough. The committee must have something to do, must be prompted to plan a progressive program.

The importance of member attendance and member participation in society activities has been neatly summed up by a Detroit doctor:

The more men who participate in the activities of the medical society, the stronger and more effective the organization becomes, and the greater the interest of the entire membership.

* * *

"WINNING WAYS WITH PATIENTS"

Early articles in this series stressed the importance of the medical assistant—the receptionist, the secretary, the nurse—in the shaping of good will for her doctor-employer.

The Canadian Medical Association now has available an attractive booklet, produced by the American Medical Association, which expands the thoughts expressed in these articles.

"Winning Ways with Patients" suggests a sound and proven pattern of good public relations practices for medical assistants. It discusses such topics as the assistant's personality, good grooming, confidences, appointment practices, telephone tactics, the waiting room, handling patients, screening callers, fees, good business practices.

A copy of "Winning Ways with Patients" may be obtained free by writing Mr. L. W. Holmes, Assistant Secretary, The Canadian Medical Association, 150 St. George Street, Toronto 5, Ontario.

GENERAL PRACTICE

THE USE OF CHLORPROMAZINE AND RESERPINE IN PSYCHOLOGICAL DISORDERS IN GENERAL PRACTICE*

H. AZIMA, M.D., *Montreal*

WITHIN THE LAST THREE YEARS, we have been witnessing the appearance of new pharmacological substances[1-4] which, according to the editorials of leading magazines and newspapers, have revolutionized the field of psychiatric treatment. According to these sources, the new drugs have provided us with psychiatric aspirins to alleviate the mental aches of patients and eliminate their psychopathology.

Unfortunately, psychiatry, as yet, cannot fulfil all these expectations. The question may arise in the minds of the general practitioners, who are professionally closest to the psychosomatic field of human complaints, as to what is the real value and true therapeutic position of these drugs, which we may designate as "psycholeptic"* and of which reserpine and chlorpromazine are the two important ones. The general practitioner may ask about the value of these drugs in his daily practice in treatment of psychologically deviant behaviour, and what he can expect from them. The purpose of this paper is to clarify, if possible, some aspects of these questions. However, before doing this, it may be worth while to discuss very briefly what these drugs are, how they are used in strict psychiatric practice, and their expected complications.

PHARMACOLOGY

Chlorpromazine and reserpine are chemically quite different. Chlorpromazine is a phenothiazine derivative chemically quite close to antihistaminic substances, such as Phenergan and Diparcol (used in treatment of Parkinsonism). It has a marked adrenergic activity, a moderate cholinergic activity, and a weak antihistaminic action. Its main effect is an inhibition of sympathetic mediated autonomic functions. It has an inhibitory effect on diencephalic autonomic structures, which regulate temperature, metabolism and other vegetative activities. It is a potent hypotensive agent and is also a valuable antiemetic.

Reserpine is an alkaloid fraction of the roots of any one of several species of plants of the genus *Rauwolfia* (named for Leonard Rauwolf, a German physician and botanist, who described this plant in 1582). Reserpine's action is also inhibitory and consists of a reduction of the activity of the central sympathetic mechanism. However, it appears that the reserpine inhibition is mediated in part through the cortex, while chlorpromazine more particularly inhibits midbrain structures. Regardless of these neurophysiological differences, both drugs have an inhibitory effect on some psychomotor and affective states of the organism, chlorpromazine being more rapid in its activity.

DOSAGE AND INDICATIONS

In psychiatric practice, chlorpromazine is used in doses from 50 to 2,000 mg. or more a day, reserpine from 0.5 mg. to 20 mg. daily. It is legitimate to say that in psychiatric cases seen in general practice the average daily dose does not need to exceed 200 mg. for chlorpromazine and 3 mg. for reserpine.

The strict psychiatric indications for these drugs are all states of excitation and tensional rise, particularly manic states and acute psychotic states associated with agitation and excitation.

We will now consider the situations in general practice where these two drugs may be used beneficially.

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*McGill University and Allan Memorial Institute, Section of Psychopharmacology, Montreal.
Read in part at the Refresher Course for General Practitioners, Royal Victoria Hospital, Post Graduate Board, Montreal, November 21-26, 1955.

*Meaning "reducing psychological tension".

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1. *Prevention of some psychotic relapses.*—This problem arises in two different situations: (a) The situation where patients live far from a psychiatric centre, or their financial means do not allow them frequent trips to these centres. In these cases, prolonged administration of reserpine or chlorpromazine over periods of years (two or more) after the patient has been discharged from a psychiatric centre may maintain an improved level of functioning, and, in some instances, may prevent the outbreak of acute episodes. The general practitioner may undertake or supervise this prolonged treatment in association with his important psychological supporting role. It should be noted that this prolonged treatment necessitates two or three visits a month, not only to give support to the patient and establish a warm relationship, but also to detect any complications that may arise. (b) The situation where the patient has not received this prolonged form of drug treatment. In some of these cases, occasionally an acute psychotic episode can be aborted if the patient is seen at the very onset of the attack and moderate doses of chlorpromazine or reserpine are given. Many patients, particularly maniacal ones who have experienced recurrences of their symptoms before, can detect the emergence of a new outbreak long before it clinically becomes evident. Drug therapy at these stages may abort the full-blown clinical picture. In some schizophrenic states the relatively sudden emergence of irrational anxieties may be the harbinger of an acute psychotic episode. Here too, drug therapy may occasionally arrest the progression of the syndrome.

2. *Pre-admission management of psychiatric cases.*—In many cases of acute agitation and excitation (manic state, acute agitated schizophrenia, agitated depression with suicidal tendencies), immediate admission to a psychiatric hospital is impossible, because of lack of beds or distance, and the patient has to wait several days. In many such cases, the ordinary sedatives and hypnotics do not and cannot control the patient, and a situation of great stress for the patient and his family may arise. In many of these cases, chlorpromazine or reserpine, alone or administered in conjunction with other sedatives, may foster a rapid decrease of agitation and excitation and a smoother period of waiting, and prevent disruption of family organization and routine.

3. *Pre-admission management of non-psychiatric cases.*—In this category we may include all those patients who are worried, and very anxious about hospitalization for causes other than psychiatric illnesses. Among these we may think of patients waiting for major surgical operations which entail some mortality and some morbidity. Psycholeptic drugs may be of some benefit in these cases. By decreasing anxiety and tension in such patients, one may be able to prepare them better for surgery, and organize a better postoperative recovery in an atmosphere of lowered anxiety and apprehension. Since chlorpromazine is used extensively in many centres as pre-anæsthetic and anæsthetic medication, in needed cases the medication may be administered a few days earlier. Anxiety arises, in some cases, in relation to anticipated mutilation or loss of an organ. Regardless of the deeper psychological significance of this loss, anxiety in itself, if intense, may hamper organized preoperative and postoperative planning of the patient's social undertakings and roles. It is conceivable that the anxiety-reducing capacity of psycholeptic substances may be used to prevent this disorganization.

4. *Management of severe somatic illnesses.*—In this category we consider especially those patients suffering from advanced and incurable cancers. Psycholeptic substances may be beneficial through their pain-reducing capacity, and as well as lessening tension and anxiety, they may permit a cooler appraisal of the situation and the development of a "let us enjoy what is left of it" attitude. What was said about the anxiety over loss of organs in surgery holds true for the total loss of the organism. If the anxiety of annihilation and death can be decreased, it is evident that life in these cases may be tolerated better and with less suffering. We know that in some instances these drugs (particularly chlorpromazine) produce a kind of blunting of experience, where the perceptions lose their sense of self-belongingness, and the harrowing nature of experience is neutralized and becomes less alarming. This kind of psychological state is, from a humanitarian point of view, beneficial for patients who harbour incurable diseases, and allows a more comfortable existence.

5. *Social anxiety.*—There has been recent evidence indicating that in states of social disorderliness, panic and agitation, administration of psycholeptic substances either to the leader or to the member of a group, or to individuals confronting a social group, will increase the managing and controlling power of the leader or member. Cases have been cited of officers in combat and judges in trial settings who, because of intense anxiety and tension, have felt unable to manage a stressful position, but under psycholeptic substances were better able to control themselves and the situation. It is conceivable that, particularly in small communities, outbursts of what can be called mass agitation and hysteria could be controlled by administration of these drugs. Pierson, a French North African psychiatrist, reported that on one occasion he was able to control the disorderliness and hysterical reaction of a small group of people who were caught in a riot by giving them small doses of chlorpromazine. He thought that the drug decreased the tension, apprehension, and hysterical reactions of each member to a suffi-

cient degree to allow the suppression of the riot.[5]

Evidently the speculative nature of these observations is stronger than their scientific value. However, they indicate the possibility of a sociological use of our psychopharmacological knowledge. It would appear that the general practitioner, who is most likely to be involved in social situations, is the one who can test these speculations and investigate their validity.

6. *Miscellaneous.*—In this category we include only two conditions, headaches and addictions. The problem of headaches is too complex to allow a unified conception, and it would be erroneous to think that these psycholeptic substances can play a major role in their treatment. But there are cases of intractable headache, in which pent-up and undischarged hostility plays a large role, where benefit may be gained from these drugs. The temporary alleviation of the headache may allow the possibility of instituting other forms of treatment, particularly psychotherapy.

As regards the problem of addiction to alcohol or otherwise, many reports have indicated the valuable contribution that psycholeptic drugs can make. They allow in many instances a rapid withdrawal, and cut down considerably post-withdrawal complications and symptoms. They are valuable also in the treatment of delirium tremens, which may become an acute emergency. In this case, these drugs are of great value to the general practitioner, who probably will see the patient first.

The therapeutic value of psycholeptic drugs in premenstrual tension states and in the management of labour may be mentioned here.

Complications

We will consider briefly those complications which are of some importance and may become troublesome.

Chlorpromazine complications.—Of these, we should mention sudden collapse because of drop in blood pressure, the treatment being simply to make the patient lie down; allergic cutaneous manifestations, which will respond to a decrease in dose or cessation of the drug; liver damage; and Parkinsonism. Alteration of liver function occurs in 5 to 10% of cases with or without jaundice. It occurs usually within the first four weeks of treatment. The histological changes are in the bile ducts, and are cholangiolitic in nature, while liver cells are not altered. The liver returns to normal shortly after cessation of the drug. We have found that one liver function test, alkaline phosphatase determination, is a fairly reliable index of liver changes in chlorpromazine therapy. If this test is repeated once a week, and if there is a gradual rise in three successive readings, there is a fair possibility that jaundice will develop, and the drug should be stopped.[6]

Parkinsonism occurs in 3 to 5% of cases, usually in the third week of the therapy. It will disappear within a month of cessation of treatment. It is always transitory, with no sequelæ.

Reserpine complications.—In addition to its general systematic effects (hypotension, stuffiness of the nose, etc.), some extra-pyramidal signs are occasionally seen which some investigators have called Parkinsonism. Actually, this does not appear to be a "true" Parkinsonism and disappears with decrease in dosage. Because of the reports of two cases of rupture of stomach by Bleuler in patients receiving reserpine, caution is recommended when the drug is used in patients suffering from gastric disturbances.[7]

Summary

To summarize, the so-called psycholeptic drugs, chlorpromazine and reserpine, have a wide variety of application, but they are by no means curative agents. They do not treat the cause, but are symptomatic medications which may arrest the evolution of some psychopathological sequence of events within a particular psychiatric syndrome, or in relation to other disorders. They are indications of a new era in psychiatric and psychosomatic therapy, but they are far from constituting the penicillin period of psychiatry. We should not let our enthusiasm accelerate unduly the vehicle of our scientific accuracy.

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MEDICO-LEGAL

CLAIM FOR NEGLIGENCE IN VACCINATION

T. L. FISHER, M.D.,* *Ottawa*

In January 1952 a pædiatrician vaccinated an 18-month-old girl on the inner aspect of the left arm. The mother drew the doctor's attention to the right thumb, which was reddened and which the mother feared might be infected. The doctor examined it and decided the reddening was not caused by infection, so he proceeded with the vaccination.

A week later the infant developed fever and what her parents considered a severe vaccination

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reaction. She was taken to and examined by the pædiatrician. He found that, in addition to a typical vaccinia reaction, she was suffering from acute tonsillitis and he instituted appropriate treatment immediately. One or two days later, during which the tonsillitis subsided, lesions appeared at the posterior border of the left axilla, on the right thumb and on the right upper cheek. These were considered "multiple takes" of the vaccination. Two weeks after the vaccination the vaccinated areas looked infected and a diagnosis of impetigo was made. Ten days later the first vaccination site was obviously secondarily infected and an ulcer was present, 1½ × 2 inches (3.75 x 5 cm.) in size, through the entire skin thickness. The infant was sick enough for the doctor to advise admission to hospital where, for a month, an acute, stormy illness caused much anxiety. Treatment was difficult and expensive and though the child recovered she had disfiguring scars on the inner arm, on the right thumb and on the right cheek.

The parents felt that something must have been wrong with the vaccination to allow or to produce such a severe illness and so much disfigurement. Through a lawyer a demand was made for reimbursement of the costs of medical treatment, an amount just less than $2,000. The demand was refused firmly by the doctor, who felt and said that the extra two "takes" had occurred in spite of usual precautions against such spread and that the secondary infection was due to an acute infection, the tonsillitis, over which he had no control and which had itself necessitated treatment. The parents were unwilling to accept this explanation and brought action against the doctor.

The case came to trial in May 1955 and the trial lasted two full days. Judgment, delivered orally at the conclusion of the evidence and argument of counsel, was given in favour of the doctor. In the judgment, the judge held that "the plaintiffs in this case have failed to make out a claim for negligence on the part of the defendant either on the ground that the doctrine of *res ipsa loquitur* applied . . . or on the evidence taken as a whole . . . the evidence on behalf of the plaintiffs did not indicate any negligence on the part of the defendant, not only did not establish such negligence but did not make out a prima facie case of negligence . . ." The judge said ". . . one could not help feeling sorry for not only the infant plaintiff but for the parents for the very great anxiety which the parents must have had and for the suffering which the child must have had as a result of the course of this ailment; but it is recognized . . . that because a course of illness or medical treatment has had untoward results that does not imply that there has been any, not only negligence but any failure of any kind on the part of the medical practitioner in respect of his treatment and conduct as a professional man." . . . "The professional person does not ensure cures or even satisfactory results or even, you might say, the expected results. All he can do is do the best he can to carry out the professional service in a proper and recognized professional manner. . . . There is always the hope that that will bring about a proper result, a cure, or a satisfactory result, but sometimes that does not happen; but, as I say, the fact that it does not happen does not mean that the doctor has not used the proper treatment or used proper care." After some discussion of some other points raised by the plaintiffs the judge finished: "To my mind this is just one of those very unfortunate occurrences for which no one can be blamed in any way, either the doctor or the parent or parents. It is most unfortunate that it happened, but those things do happen. The action must, therefore, be dismissed."

The parents were not satisfied and instituted an appeal which was heard in February 1956. The hearing occupied a full day and a few days after its conclusion judgment was rendered. The court summarized the basis of the claim and then stated the two points on which plaintiff's counsel based their allegation of negligence: "(1) that the defendant was negligent in selecting as the site of vaccination the inner aspect of the infant plaintiff's left arm rather than the point of insertion of the deltoid muscle on the outer aspect of the arm, and (2) that the defendant was negligent in carrying out the vaccination at a time when, to his knowledge, the infant plaintiff had a sore or inflamed right thumb."

The Court discussed the various sites available for vaccination, mentioned some of the reasons for vaccination in one or another place and concluded by saying:

> "The evidence accepted by the learned trial judge substantiated the defendant's averment that he had acted in accordance with standard and recognized practice in selecting the vaccination site chosen by him in this instance.
>
> "As to the second or alternative allegation of negligence, I am bound to say that the evidence fails to support it. There is no doubt but that the presence of skin lesions, and especially diffused skin lesions, eczema, or the presence of infection are contraindications to vaccination, but the record discloses no evidence which would warrant a finding that any contraindications of the nature described existed or were discernible on the date of the vaccination. The mother of the child stated that she called the defendant's attention to her daughter's right thumb which, she said, presented a red or inflamed appearance. The defendant concluded after he had examined the digit that the reddening was due to a slight irritation, such as might be caused by thumb sucking, and he decided that there was no infection in the thumb. While the mother informed him that her child had not acquired this habit, the doctor, knowing that many young children indulged in the habit surreptitiously at night without their parents' knowledge, was not too greatly impressed by the mother's assertion, which probably merely reflected a fond maternal pride. There is no foundation in the evidence to support the contention that the defendant erred in arriving at this

conclusion and there is far less to suggest that in making this diagnosis he did not have the knowledge or that he failed to exercise that degree of care and skill which the plaintiffs were entitled to expect of a medical practitioner in his position."

". . . In this case, however, the evidence makes it abundantly plain that the real cause of the infant plaintiff's illness was a secondary infection by a form of bacterial coccus known as streptococcus or staphylococcus or by a combination of them."

Then followed a discussion of "the legal principles bearing upon the degree of care and skill which may be expected of physicians or surgeons" in which the judge said "I do not believe that that standard of care has been more clearly or succinctly stated than by Lord Chief Justice Hewart in Rex v. Bateman (1925) 41 T.L.R. 557; from which I quote:

"'If a person holds himself out as possessing special skill and knowledge and he is consulted, as possessing such skill and knowledge, by or on behalf of a patient he owes a duty to the patient to use due caution in undertaking the treatment. If he accepts the responsibility and undertakes the treatment and the patient submits to his direction and treatment accordingly, he owes a duty to the patient to use diligence, care, knowledge, skill and caution in administering the treatment. . . . The law requires a fair and reasonable standard of care and competence.'

"Each case must, of course, depend upon its own particular facts. If a physician has rendered treatment in a manner which is in conformity with the standard and recognized practice followed by the members of his profession, unless that practice is demonstrably unsafe or dangerous, that fact affords cogent evidence that he has exercised that reasonable degree of care and skill which may be required of him. It has not been made to appear that the defendant physician departed in this instance from what has been established to be the standard and recognized practice of physicians in this province. The plaintiffs have failed to satisfy the burden of proving any negligent act or default on the part of the defendant or that the infant plaintiff's illness and accompanying distress occurred in consequence of any such act or default.

"It is trite to say that it is always easy to be wise after an event, and in cases of this kind care must be taken not to condemn as negligence what may be, and in this case undoubtedly is, only a misadventure. Nothing is to be imputed to the defendant that is not clearly proven against him. *Post hoc, ergo propter hoc,* has no place in our law.

"It follows from what has been stated that I would dismiss this appeal with costs."

MEDICAL SOCIETIES

SECTION OF PHYSICIANS IN PUBLIC SERVICE, C.M.A.

Salaried and/or employed physicians will be pleased to learn that a new section of the Canadian Medical Association was formed last year to facilitate dealing with the manifold problems which confront this particular group of doctors. This section is known as "Physicians in Public Service". It is so named since most of its members are professionally engaged in public medical institutions of one sort or another.

An ever-increasing proportion of physicians in Canada are not completely self-employed. In addition to the usual problems of medical practice these physicians, in many instances, are faced with other factors, such as employer-employee relationships. In the complexities of this modern civilization this group frequently finds that sound medical opinion is ineffective in the face of increasing lay influence at administrative and legislative levels.

With these facts in mind this section has been formed with the following objectives in mind:

1. To act as an authority on medical matters concerning employed physicians and to make recommendations concerning these matters to the Council of the Canadian Medical Association.
2. To maintain a high standard of proficiency amongst employed physicians.
3. To elevate the scientific and professional status of the employed physician.

All of these aims can be obtained if we have a strong section working with and through the Canadian Medical Association.

All members of the Canadian Medical Association who are not completely self-employed are strongly urged to attend the meeting of this section at the Annual Meeting of the Canadian Medical Association. The section will meet in Room 19 of the School of Commerce at 9.30 a.m. on Thursday, June 14.

H. G. PRITZKER, B.A., M.D., Chairman,
Section of Physicians in Public Service.

AMERICAN COLLEGE OF PHYSICIANS

The 37th annual meeting of the American College of Physicians, held in Los Angeles from April 16 to 20, was of interest to Canadians for several reasons. In the first place, the meeting itself is one which is enjoying increasing prestige as a forum in which the best-informed clinical opinion is expressed on a wide variety of subjects in an extremely varied way.

In the second place, the President this year was Dr. G. F. Strong of Vancouver, past president of the C.M.A. He carried his honours lightly, and performed his duties with the air of friendliness and dignity which seems to characterize him. The meeting was a great success and he and his executive are to be congratulated.

In the third place, the contribution of Canadian Fellows to the program was not inconsiderable, either in volume or quality.

The meeting was held in the huge Shrine Auditorium. The scientific program was well organized and varied, consisting of morning lectures of a comprehensive type, afternoon sessions made up of papers of briefer but more searching compass, and panels on a wide variety of timely subjects. These were informal but informative, and provided the only opportunity for give-and-take discussion between the experts and their audience.

Clinics given at the various local hospitals were seen on closed-circuit television circuits at the Auditorium, partly as a concession to the geographic immensity of Los Angeles (euphoniously abbreviated to LAX on the air line labels), and partly as a means of exploring the possibilities of TV as an educational tool. There were facilities here, too, for the transmission of questions from the audience to the participants, but there was still an aura of remoteness which detracted from the immediacy of the discussion.

It was impossible for one person to savour all these delicacies, particularly when there was a silent but tempting display of scientific and commercial exhibits to occupy idle moments. It is also impossible to select the most noteworthy contributions, since this is so much a matter of individual interests and taste.

To begin with the Canadians, Professor R. V. Christie of Montreal presented a lucid and persuasive account of the factors involved in the genesis of emphysema and the disability which it produces, and emphasized the part which bronchospasm frequently plays. He discussed the means whereby this component can be evaluated in

an individual patient, and pointed out the therapeutic importance it has, once it has been identified. Dr. J. Genest, also of Montreal, discussed the work which had been done, both in Montreal and Toronto, which appeared to implicate aldosterone in the production of hypertension. Dr. K. Evelyn, of Vancouver, gave a scholarly lecture on the whole concept of hypertension, its natural history and the means of studying it, in which he countered the hypothesis put forward by Professor Pickering at last year's meeting that essential hypertension is really an aggravation of a normal tendency in some families, hardly to be dignified with the status of being a nosological entity. A similar lecture by Dr. A. J. Rhodes of Toronto on newer work in the diagnosis of virus diseases was also extremely illuminating and interesting. Dr. S. L. Borduas of Montreal took part in one of the televised clinics from the Cedars of Lebanon Hospital, Dr. Bram Rose of Montreal was on a panel discussing the uses of cortisone, and Dr. Don Wilson of Edmonton was on a panel dealing with endocrinological problems. A paper on the use of cortisone and a gluten-free diet in the treatment of primary and secondary sprue was presented at one of the afternoon sessions by Dr. K. J. R. Wightman of Toronto.

The American College bestows two prizes annually on people who seem to have advanced medical learning in a signal way. It is food for thought that this year neither of the laureates was a physician. The John Phillips Award went to Dr. Linus Pauling, a biochemist, who gave a lecture on his researches into sickle cell anæmia, and the other inherited abnormalities of hæmoglobin, which he put forward as examples of disease produced by an alteration in the synthesis of a single molecule in the body, a situation to which he gave the name "molecular disease". Such a biochemical lesion might be expected to occur in a variety of clinical settings, particularly in the field of congenital or familial disease, and the whole concept is novel and interesting.

The James D. Bruce Memorial Award went to Dr. John F. Enders, a bacteriologist, who gave a lecture on the "Present Status of Etiologic Discovery in Human Viral Diseases", which overlapped a good deal with what Dr. Rhodes had said, but which attested to the tremendous contribution he has made in the techniques and elucidation of the newer information regarding viruses.

Dr. Macdonald Critchley was guest lecturer from London, England, and was called upon to give an after-dinner speech, an address to Convocation, and a scientific presentation on "Constitutional Insensitivity to Pain"—a syndrome which might enable one to bite off an injured finger or undergo an operation for cataract without anæsthesia, but otherwise live a fairly normal though uneventful existence, without evidence of neurological disease. His discourses were witty and entertaining, but did not conceal his deep scholarship and penetration.

From this point, the writer must pursue his own bent. One paper which was most impressive concerned the problem of non-obstructive pyelonephritis, a disease which was presented as being much commoner than most of us realize, and impossible to diagnose if one depends on the classical urinary findings as a criterion. In the view of the speaker a persistent bacilluria was sufficient evidence upon which to base a diagnosis, and he emphasized the importance of treating it with bactericidal antibiotics wherever possible, and making sure that the urine was sterilized.

A panel on subacute bacterial endocarditis was most emphatic regarding the necessity for a bacteriological diagnosis in planning therapy, but agreed that in the use of antibiotics the implications were more quantitative than qualitative. In other words, penicillin and streptomycin are preferred even though the organism appears to be sensitive to bacteriostatic antibiotics such as tetracycline. Combined therapy with five million units or so of penicillin and two grams of streptomycin daily was advocated in all cases of *Streptococcus viridans* endocarditis in which the organism was sensitive to 0.1 unit of penicillin or less. In such cases it might be safe to discontinue treatment in as little as two weeks. With more resistant organisms, immense doses of penicillin were given, the streptomycin carried on for only two weeks, and the total duration of therapy four to six weeks.

Reports on the quantitative aspects of quinidine therapy, the use of sitosterol as a means of reducing the blood cholesterol and lipid values in atherosclerosis, the transplantation of parathyroid tissue in cases of tetany, were all of interest from a therapeutic point of view. Other papers emphasized the use of new diagnostic criteria and the possibilities of new techniques in the evaluation of normal and abnormal function of many organ systems.

It is presumably also incumbent on a reporter to register certain areas of disapproval. Some of the papers were more irritating than stimulating—one sensed at times an undue acceptance of laboratory criteria as evidence of specific disease. Some of the panels were disappointing, inasmuch as they seemed to fail to come down to the crunch of clinical application and failed to define their terms of reference in a useful way. These criticisms are inevitable in a large program, and probably mainly personal.

The entertainment provided, both for the members and their wives, was memorable indeed, and one can prophesy with confidence that this first meeting in LAX will not be the last. K.J.R.W.

CANADIAN ACADEMY OF ALLERGY

The Canadian Academy of Allergy announces that it will hold a graduate course on allergy in connection with the Annual Meeting at the School of Commerce, Laval University, Quebec, on June 12 and 13. The Academy will welcome any member of the C.M.A. to these sessions. The program is as follows:

TUESDAY, JUNE 12—GRADUATE COURSE:
Morning Session: Introduction and welcome, B. Rose; Basic principles, J. Leger; Skin testing and other clinical methods, J. Roy; Rhinitis, G. Casgrain; Bronchial asthma, J. Leger.
Afternoon Session: Urticaria, J. Denis; Pædiatric allergy, H. Bacal; Therapeutics—Specific, J. Roy; Nonspecific, G. Casgrain; Hormonal, B. Rose.

WEDNESDAY, JUNE 13—SCIENTIFIC PROGRAM:
Morning Session: Aspirin Sensitivity, C. H. A. Walton, Winnipeg; Changes in the Blood Cell and Marrow Morphology, and Serum Protein Fractions in Induced and Spontaneous Allergic States, J. D. L. FitzGerald, Toronto; A Contribution to the Management of Chronic Urticaria, John H. Toogood, London, Ont.; The Nature and Origin of Fibrinoid, Robert H. More, Professor of Pathology, Queen's University, Kingston; The Pathological Physiology of Asthma, F. C. Lowell, Associate Professor of Medicine, Boston University School of Medicine, Boston, Mass.
Afternoon Session: Round Table on Allergy. Chairman, B. Rose. Participants: F. C. Lowell, Jacques Leger, H. Bacal, G. Casgrain, C. H. A. Walton, and H. Mitchell.

CANADIAN DERMATOLOGICAL ASSOCIATION

The Annual Meeting of the Canadian Dermatological Association will be held in Quebec City at the time of the C.M.A. meeting. A clinical session, for members only, will be held at the Hôtel-Dieu de Québec Hospital on Thursday, June 14. The other sessions will be held at Lac Beauport on Friday and Saturday, June 15 and 16.

Association Notes

COMMITTEE ON TRAFFIC ACCIDENTS

THE COMMITTEE on Traffic Accidents of the Canadian Medical Association met in the Board Room of the Montreal General Hospital on Friday and Saturday, April 20 and 21, with Dr. Harold Elliott in the chair. As a result of their deliberations, the General Council of the Canadian Medical Association will be asked at the annual meeting in June to approve the following resolution:

> That this Committee wholeheartedly endorse the establishment of a Canadian Medical Traffic Accident Research Foundation, and recommend to General Council that this Committee, with power to add, be instructed to proceed with application for a Charter for the Foundation.

It is understood that the following bodies—L'Association des Médecins de Langue Française du Canada, The Royal College of Physicians and Surgeons of Canada, and The Canadian Bar Association—have expressed sympathetic interest in the establishment of such a Foundation.

If Council approves this activity, the Canadian medical profession will have taken a step which so far has not been taken by any other organized medical group in the world. The purpose of the proposed foundation is, through the collection of data and their analysis, to assist in lowering morbidity and mortality due to traffic accidents. It is felt that the epidemiological approach so successfully adopted in the past in reducing mortality from infectious diseases may fruitfully be applied to the solution of the problems which the modern use of automobiles has raised.

At this meeting the following members of the Committee were present: Dr. T. R. Harmon, British Columbia; Dr. J. P. Moreau, Alberta; Dr. C. H. Andrews, Saskatchewan; Dr. C. A. R. Gordon, Manitoba; Dr. C. M. Johnston, Ontario; Dr. C. Bertrand, Quebec; Dr. D. G. Cameron, Quebec; Dr. E. F. Crutchlow, Quebec; Dr. G. W. Halpenny, Quebec; Dr. B. L. Jewett, New Brunswick; Dr. A. L. Murphy, Nova Scotia.

The following observers were also present: Dr. John O. Moore, Automotive Crash Injury Research Project, Cornell Medical College, New York; Drs. S. T. Adams, Montreal; T. E. Dancey, Montreal; C. Gardner, Montreal; S. S. B. Gilder, Toronto; J. Gillingham, Edinburgh, Scotland; Renaud Lemieux, Quebec; F. C. MacIntosh, Montreal; A. H. Neufeld, Montreal; A. F. W. Peart, Toronto; Arthur Powers, Hull; A. Ross, Montreal; T. C. Routley, Toronto; W. F. T. Tatlow, Montreal, and Mr. L. W. Holmes, Toronto.

The meeting began with a report from each of the provincial representatives on recent activities of provincial committees on traffic accidents. Most committees had met and discussed the problems involved, and in several instances had gone further and framed suggestions for further study. Dr. Harmon mentioned various points which had been considered in British Columbia. He emphasized the need for education of school children and for co-operation of the medical profession with the police in settling problems of traffic accidents. He also stressed the significance of consumption of alcohol, a common factor in fatal accidents. Dr. Moreau said that his committee had drawn up a new form for medical examination of applicants for chauffeurs' licences and had also reviewed a series of 175 fatal accidents. Dr. Murphy was particularly concerned about the defects of medical management of victims of traffic accidents. He felt that the medical profession could do much good work in training residents physicians in the handling of trauma, and in improving the quality of ambulance services. Dr. Johnston's committee had made quite a number of suggestions for study. These included a study of physical impairment of persons involved in accidents, research into the psychological qualities of drivers, testing for impairment due to alcohol consumption, rapid screening tests for applicants for licences, competence of examiners, examination of chronic offenders, study of successful enforcement policies elsewhere, automobile design, etc. Other members gave their experience with traffic authorities in their province, which indicated a co-operative spirit in attacking problems of traffic accidents.

Cornell automotive crash injury research project.—Dr. Moore's report on this project and his many helpful suggestions during the meeting were of the utmost value to members of the committee. Dr. Moore mentioned that the crash research program in the U.S.A. had started with none of the advantages which the Canadian organization already had. He felt that because of the widespread support for the movement in Canada, development should be more rapid and effective than it has been in the U.S.A. He suggested that the attack on the problem from the medical viewpoint should be made from three directions. In the first place, medicine had a role to play in preventing accidents, though this was not its primary function. In prevention, medicine had to consider such things as the rules for licensing drivers and the counselling of patients with some physical or mental disability as regards driving. Secondly, medicine had a role in preventing injury, although this again was only partially in the medical field. In the U.S.A. 10 states were co-operating on projects designed to prevent injury. The primary function in his project was the collection of data. Thirdly, medicine had a role in the treat-

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ment of the injured; in this phase, medicine was involved alone, and any efforts at lowering mortality from automotive crashes were entirely the responsibility of the profession. Dr. Moore stressed the need for uniformity in collecting data. All units co-operating with the co-ordinating body must follow exactly the same lines. Because the Canadian approach to the problem was on a much broader basis than the Cornell project, Dr. Moore did not consider that any work done in Canada would be a duplication of work elsewhere. The project must be organized on a university basis and a national level. The approach must be not only statistical but also educational.

After the committee had agreed to recommend to Council the establishment of a Canadian Medical Traffic Accident Research Foundation, there was a considerable discussion of its framework. This has already been outlined in a paper by Dr. Harold Elliott in the April 1 issue of the *Canadian Medical Association Journal.* It was brought out very clearly at the meeting, however, that the Foundation was only part of the Canadian program for solving problems of traffic accidents. There would still be a need, as in other enterprises, for work at a national, provincial and local level. It was therefore essential that the national and provincial committees should continue their work. There would be many problems which could be best solved at the provincial level, nor was there need to wait until the Foundation was established before local and provincial committees got busy.

A second resolution was brought forward:

That C.M.A. Divisions be asked to survey the medical aspects of traffic accidents in their area and take such action as they see fit to improve the medical care of the injured in that area, and report back to the Central Committee on Traffic Accidents at its next meeting.

The members of the Committee were entertained at luncheon on Friday at the Montreal General Hospital and later escorted round the building by the Medical Director, Dr. William Storrar. The excellent luncheon was presided over by Mrs. Isobel MacLeod, Director of Nursing, and Miss B. G. Herman, Assistant Director of Nursing. In the evening members of the committee were entertained at dinner at the St. Denis Club with Dr. Claude Bertrand, the Montreal neurosurgeon, in the chair. The following spoke after the dinner: Dr. T. C. Routley, who outlined various activities which the Canadian Medical Association had in the past instigated, Dr. Moore, Dr. Halpenny and Dr. Harold Elliott. Before the dinner Mr. L. W. Holmes had convened a press conference, which was well attended by Montreal journalists and was responsible for considerable publicity for the meeting, both in Montreal and other Canadian centres.

CORRESPONDENCE

ACTH POTENCY

To the Editor:

The introduction of the Second International Reference Standard for assaying corticotrophin preparations has made it desirable to revise the declaration of potency of these preparations in order to differentiate those intended for intramuscular or subcutaneous administration from those intended for intravenous use.

Up to the present, corticotrophin preparations have been standardized against the First International Standard, using the adrenal ascorbic acid depletion method of assay in which the hormone is injected intravenously into the test animals.

During the last few years, it has been learned that the biological activity of some corticotrophin preparations is dependent upon the route of injection. In some preparations there are differences between the potency declared on the label when the drug has been assayed by intravenous injection, and the clinical activity when it is given by intramuscular or subcutaneous injection.

A revision of the corticotrophin regulations is under consideration in order that corticotrophin intended for intravenous use only, is assayed by an "intravenous" method, and that a preparation intended for subcutaneous or intramuscular use only, is assayed by a "subcutaneous" procedure. However, for those preparations which according to the label may be used by subcutaneous, intramuscular or intravenous injection, the ratio of the activity by the "subcutaneous" method to that by the "intravenous" method must not be less than 0.8 and not more than 1.25.

It is hoped that these amendments to the corticotrophin regulations will clear up much of the confusion which exists at the present time between the potency stated on the label and the actual clinical activity by any route of administration.

J. R. MACDOUGAL, M.D.,
Chief Medical Officer

Food and Drug Directorate,
Department of National Health and Welfare,
Ottawa, Ont.,
April 30, 1956.

MENTAL HEALTH

To the Editor:

May I disagree with some points raised by Dr. M. Prados in his address "On Mental Health," published in your April 15 issue.

It is time surely that the wholly discredited notion of Freud's about man "forced to live in society" was quietly and finally dropped and with it those fairy tales of man forgoing his primitive desires and ideas to fit in with society. So far as we know, men have always been gregarious and would perish if solitary. Freud was certainly in conflict with 19th Century Vienna but to puff this up into a universal condition was an error. The complicated relationship between the individual and society is in no way elucidated by this idea of an "innate conflict" which as Ruth Benedict and many other anthropologists have shown is foreign to many cultures.

Can't we scrap the prenatal Nirvana myth which has been handed down religiously in the canons of psychoanalysis? From what we know the embryo is the product of the ovum and the survivor of one in several million sperms. From conception to parturition it enters a series of rapid, continuous and, what is more, dangerous changes. I understand that about 25% of embryos

do not survive this astounding co-ordinated climb up the phylogenetic ladder. Observations show that babies kick, struggle and it is even said cry out *in utero*. I can find little evidence that the womb is the Nirvana, the place where all desire ceases. The evidence that we have suggests that it is more like primordial chaos, a crucible of potentials. Birth is certainly another period of great change, but is it any more terrifying than conception? If Dr. Prados is correct in supposing that socialization is an attempt to regain the Nirvana-womb state, then one would expect viviparous animals to be gregarious. Observation shows that this is not necessarily so. Furthermore, many oviparous creatures are highly gregarious. So that the biological basis of this hypothesis is faulty.

This psychiatrist, at least, is not "now convinced that heredity does not play the important role in the etiology of mental illness that traditional medicine had thought and accepted for centuries". The studies of Franz Kallman and Eliot Slater show that heredity does play a major part in predisposition to schizophrenia. What is the point of misleading people? I cannot see why it should be considered a sign of optimism to deny that hereditary endowment is often of great importance. If we learn how to recognize this early enough, we may be able to do something about it.

By ascribing mental illnesses which may well be due to endogenous and inherited biological error to the shortcomings of parents, siblings, teachers and others, one simply builds up more fear in the tens of thousands of "mothering ones" (to use Harry Stack Sullivan's vivid phrase) and this will in fact induce anxiety in their babies. So by denying the inherited component which the evidence suggests exists, Dr. Prados, in his mental health teaching, will make mothers fearfully preoccupied with whether through not loving their children enough, or too much, they are pushing them towards psychoses. While I do not deny that unkind parents may make the development of a schizophrenic illness more likely in a predisposed child, I do not think that neglect and unkindness in early infancy has been proved to have any clear relationship to schizophrenia. I doubt whether, as the parent of a schizophrenic child, I would find it consoling to know that I need not fear an inherited disorder because the ailment might be due to "toxicosis, infections, traumata and so on".

While applauding Dr. Prados's belief that public education is both necessary and desirable, I do not feel that he has set a very good example. Who, one wonders, will educate the educators? These *jeux d'esprit* of early Freudism are not good enough in the centenary of Freud's birth. Psychoanalysis, like any other established discipline, must grow up and be its age.

HUMPHRY OSMOND, M.D., M.R.C.S., D.P.M.

Box 1056,
Weyburn, Sask.,
April 24, 1956.

RABIES

To the Editor:

In the editorial, "Rabies in Canada" *(Canad. M. A. J.*, 74: 566, 1956), it is stated that "the indications [for treatment] must be weighed carefully and the treatment with vaccine not undertaken lightly." Quite true. Thus, those weighing the indications should know, firstly, that the efficacy of post-infection vaccine prophylaxis is far from unequivocally established and that there is reason to doubt that it has any value. Secondly, they should know that rabies has been produced (in calves) with phenolized vaccine that had passed all prescribed tests for innocuity; that, since the tests for innocuity used today may also fail to reveal live virus, it is quite possible that live virus persists for some varying time in all such phenolized vaccine; and that any efficacy the vaccine may have may be due to the content of live virus. While the presence of live virus does not necessarily constitute much of a hazard in the doses used in vaccination, every physician should know what he is using. Further, as experimental rabies has been produced in rats under conditions which eliminated the possibility of neural transport of the virus, it is possible, and much ancillary evidence so suggests, that in all rabies the virus is transported from the injury to the central nervous system by the blood stream rather than along nerve paths. This point is of some significance in consideration of post-infection vaccine prophylaxis. The factual findings mentioned above have been made by different workers but, to the writer's knowledge, have never been presented in medical journals or textbooks. They are, however, fundamental to any competent consideration of rabies.

N. E. MCKINNON, M.B.

Dept. of Epidemiology & Biometrics,
School of Hygiene,
University of Toronto,
150 College Street,
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April 17, 1956.

SPECIAL CORRESPONDENCE

The London Letter

(From our own correspondent)

HEALTH CENTRES

The Minister of Health has informed the London County Council that he sees no advantage in providing health centres in an area where the existing arrangements for giving service are adequate. *Sic transit gloria.* Once again the dogged individualism of our race has asserted itself, and the armchair planner has had to return to his inner sanctum to think again. In the medical planners' heyday preceding the inauguration of the National Health Service, health centres were the *sine qua non of* successful general practice. Experience has shown that this is far from being the case. There is undoubtedly a place for such centres, and there is general agreement with the Minister that this is in large-scale new housing estates. In the Minister's opinion these are the only areas in which there is scope for health centres. Even in such areas, however, he will not authorize a new health centre unless its purpose is to secure close association of the local health authority services with general practitioners.

This decision of the Minister is in conformity with the experience of the London County Council, which has encountered considerable difficulty in persuading local practitioners to make use of a large health centre which the Council erected at considerable expense. One of the arguments against so doing is that there is no protection for the practice of a doctor who goes into a health centre. If he closes his own surgery another doctor may set up practice in the neighbourhood. The only way to counteract the loss of practice that this may involve is to maintain his existing surgery on moving into the health centre, thus adding considerably to his overheads. After a careful review of the situation the Council has come to the conclusion that group practice is an easier and more satisfactory method of attaining many of the advantages claimed for health centres.

MARRIAGE AND DIVORCE

Acceptance by a wife of artificial insemination by a donor without her husband's consent is equivalent to

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adultery and should therefore be recognized as a ground for divorce, according to the recently published report of the Royal Commission on Marriage and Divorce. It is also recommended that consent to a wife's artificial insemination, whether with semen from the husband or a donor, should be a bar to proceedings by either spouse for nullity on the grounds of impotence. The Commission rejects the suggestion that lesbianism should be a specific ground for divorce, on the bases that the word is used to describe the whole range of female homosexuality and does not refer to a specific act; the difficulty of proof; and because in some circumstances lesbianism is already held in divorce proceedings to amount to cruelty. The view is expressed that insanity should no longer be a good defence against a charge of cruelty in divorce proceedings.

High School for Cripples

In September this year, at the Lord Mayor Treloar Training College, at Alton in Hampshire, a special school is to be opened which will make provision for able and gifted physically handicapped boys. The school, which will be the first of its kind in this country, will have accommodation for about 70. Boys will be admitted at any time from the age of 11 and will receive a full-time general education up to the age of 16, with some general introduction to technical work. At the age of 16, it will be possible to transfer to one of the vocational courses already provided by the College in virtue of the fact that it is a training establishment for the training of physically handicapped pupils. As an alternative to vocational training, it is hoped to develop an academic course for boys likely to benefit from this, should there be sufficient demand.

Orthopædic Museum

The latest benefaction of the Wellcome Trust is the grant of £4,500 for the establishment of the Wellcome Museum of Orthopædics of the Institute of Orthopædics at the Royal National Orthopædic Hospital. The main function of the museum, which was formally opened on April 4, is to assist postgraduate teaching. Part of its function, however, will be to show the results of current investigations, especially those carried out at the Institute.

An Octogenarian Orthopædic Surgeon

Two ceremonies have marked the 80th birthday—on March 28—of Sir Thomas Fairbank, the doyen of British orthopædics. One was the publication of the February issue of the *Journal of Bone and Joint Surgery* as a special "Thomas Fairbank Birthday Volume". The other was the presentation to him of his portrait as a gift from his former house surgeons and colleagues at King's College Hospital. Sir Thomas Fairbank, who was trained at Charing Cross Hospital, became orthopædic surgeon to King's College Hospital and The Hospital for Sick Children, Great Ormond Street. Out of this latter association arose his outstanding contributions to the treatment of congenital dislocation of the hip. Perhaps his most permanent contribution to orthopædics will prove to be his "Atlas of General Affections of the Skeleton", published in 1951. WILLIAM A. R. THOMSON

London, May 1956.

ABSTRACTS *from current literature*

MEDICINE

Survival of Diabetic Patients after Myocardial Infarction.

R. F. BRADLEY AND J. W. BRYFOGLE: *Am. J. Med.*, 20: 207, 1956.

Coronary artery disease has in recent years produced nearly one-half of all deaths in diabetic patients. Preliminary observations on a large sample of hospitalized diabetic patients indicate its presence in over 40%. The presence of diabetes mellitus has been associated with high mortality from acute myocardial infarction: 60.8% after all attacks and 57.8% after the first attack. Thus the diabetic with acute myocardial infarction has a prognosis similar to that of "poor risk" cases from the general population. The high incidence of and mortality from myocardial infarction in diabetic women contributed measurably to the poor experience.

That diabetes per se played a major part in early mortality, particularly as a result of its effect upon women, was shown by the 60% early fatality rate for the series of women who did not have angina, hypertension, obesity, heart failure or previous myocardial infarction. On the other hand, an early mortality of 8.3% was found for men in whom these factors were absent.

Late survival of diabetic patients after the initial attack of myocardial infarction was also decreased, since fewer than 20% lived five years and only 3.6%, ten years.

Early death occurred in all of 11 diabetic subjects having marked hyperglycæmia and acidosis with or without ketosis. Although each experienced "shock", it could not be shown that changes in carbohydrate metabolism were directly related to the presence of shock or to histological changes in the liver at autopsy.

S. J. SHANE

Epidemiologic Studies on Antibiotic-Resistant Strains of Micrococcus Pyogenes.

R. I. WISE, C. CRANNY AND W. W. SPINK: *Am. J. Med.*, 20: 176, 1956.

It is evident from published reports, and from the findings at the University of Minnesota Hospitals and the Minneapolis General Hospital, that strains of staphylococci recovered from persons outside a hospital or those who have not received an antibiotic differ from those obtained from patients in a hospital and from hospital personnel. A high percentage of the former are susceptible to the action of antibiotics whereas "hospital" strains possess considerable resistance to most of the antibiotics. Resistance to each antibiotic is roughly correlated with the quantities of antibiotics used.

Infections with antibiotic-resistant strains occur as a result of two mechanisms: (1) the emergence of resistant strains from more sensitive strains by a given antibiotic selecting resistant cocci, thus permitting their survival and multiplication; (2) cross-infection by strains previously resistant to antibiotics.

Antibiotic-resistant strains predominate in the hospital environment as a result of a selective process of antibiotic action. These resistant strains are carried by patients and by members of the hospital personnel. Highly resistant strains infect wounds and cause pneumonia and genitourinary tract infections; in some cases, septicæmia ensues, often with fatal results.

A great need exists for an awareness of the nature and magnitude of this problem. The ubiquity of the pathogenic antibiotic-resistant strains of staphylococci in the hospital environment indicates the need for prophylactic measures to prevent cross-infections of patients and the establishment of the carrier state in members of the hospital staff. S. J. SHANE

Reactivation of Inactive Pulmonary Tuberculosis.

J. KATZ, S. KUNOFSKY AND B. LOCKE: *Am. Rev. Tuberc.*, 73: 31, 1956.

For many years there has existed a controversy as to whether reinfection tuberculosis is exogenous or endogenous. Certainly it is of great importance to know whether extensions of tuberculous disease in sanatorium patients may or may not be brought about by exposure to other patients with open tuberculosis. To date, it has been impossible to state with any degree of finality whether a patient with active pulmonary tuberculosis may become "superinfected" by contact with another who has open pulmonary tuberculosis. This paper, while it does not answer this very urgent question, deals, at least indirectly, with the question of reactivation of *inactive* pulmonary tuberculosis from exogenous sources.

A group of mental patients was studied who had been found to have pulmonary tuberculosis during the conduct of a tuberculosis control program in the 18 mental hospitals of the New York State Department of Mental Hygiene. The period covered in this report is 1941-1952. Grouping of all patients with inactive tuberculosis by residence either in tuberculosis wards or in general wards was possible only in two hospitals; and the results indicated that the reactivation rate in hospitals with tuberculosis wards was 64% greater than in those without such wards. The association of exposure and reactivation was further demonstrated by the results in two hospitals in which patients with inactive tuberculosis were housed both on tuberculosis wards where exposure to infectious tuberculosis was greater, and on general wards where exposure was less. In one such hospital, reactivation rates were more than twice as high among residents on the tuberculosis wards as among those on the general wards; while in the other, the reactivation rates were more than five times as high among patients in the tuberculosis division of the institution as among those in the rest of the hospital. These differences all proved to be statistically significant.

From this study, therefore, it appears that exposure of patients with inactive tuberculosis to cases of infectious tuberculosis increases the probability of reactivation.

S. J. SHANE

SURGERY

Treatment of Unexpected Cardiac Arrest by External Electric Stimulation of the Heart.

P. M. ZOLL *et al.*: *New England J. Med.*, 254: 541, 1956.

Cardiac arrest occurs in one in every 500 to 5,000 operations. It is usually due to cardiac standstill, rarely to ventricular fibrillation, and still more rarely to complete atrioventricular block.

Every hospital should have a prearranged program of resuscitation for dealing with cardiac arrest. This program must be well organized, frequently rehearsed and ready for immediate application. Such a program resulted in the survival of five of eight cases treated by the authors. A cardiac "monitor" is necessary for immediate indication of cardiac arrest, the best type being one which registers the electric activity of the ventricles by an audible signal of each heart beat and also sounds an automatic alarm with cessation of cardiac pulsation. On the occurrence of such an alarm an external electrical pacemaker should be in action within one minute. Artificial respiration with oxygen is always necessary as an adjunct to treatment. Other auxiliary measures which may be needed are intravenous infusions of blood or other fluids and vasopressor drugs.

After resuscitation from cardiac standstill constant observation of the patient for a period of two or three days is essential because of the likelihood of recurrence. The electric pacemaker should be kept attached and ready for instant use.

NORMAN S. SKINNER

Lumbar Sympathectomy for Arteriosclerosis.

E. A. EDWARDS AND C. CRANE: *A.M.A. Arch. Surg.*, 72: 32, 1956.

Five years after lumbar sympathectomy for arteriosclerotic disease of the lower limb, the results in 100 patients were assessed; 27 of them were diabetic and 39 had other serious disease, especially of the heart.

Sympathectomy is done at the Peter Bent Bingham Hospital for chronic ischæmia and for limbs that are "fairly sick", not only for imminent gangrene, and not for every case of arteriosclerosis of the lower limb. A short preoperative history is associated with a high amputation and death rate. Only 3 out of 63 patients with unilateral sympathectomy who survived five years lost a limb. Contralateral sympathectomy is advised if signs of vascular degeneration, particularly claudication, are noted later.

Of the 100 patients, 35 died within five years, most of coronary heart disease. Diabetes and general ischæmia (rather than local areas of necrosis) proved poor prognostic signs. Most results were good, especially among the five-year survivors. If the limb survived the first few months after sympathectomy, the favourable effects were retained.

There are two types of arteriosclerotic patients: (1) with relatively localized arterial involvement and slow progression, responding well to sympathectomy, and with a good life expectancy; (2) with diffuse arterial involvement of rapid progression, doing poorly after sympathectomy, and with a poor life expectancy.

Regarding technique, moderate dependency of the affected limb, avoidance of fall in blood pressure during and after operation, and the use of heparin postoperatively in severe ischæmia are mentioned.

BURNS PLEWES

OBSTETRICS

The Endometrial Aspiration Smear: Research Status and Critical Value.

E. L. HECHT: *Am. J. Obst. & Gynec.*, 71: 819, 1956.

A study has been made of the endometrial aspiration smear in order to determine its accuracy in diagnosis of endometrial cancer. The results have shown the clinical value of this procedure, which reflects even very early malignant changes. In addition, it indicates early hyperplastic changes in the endometrium, and the diagnosis of endometrial hyperplasia made on the basis of endometrial aspiration smears has been validated. It is advocated as a routine preliminary procedure in the investigation of abnormal uterine bleeding.

ROSS MITCHELL

Experience with Radioactive Colloidal Gold in the Treatment of Ovarian Carcinoma.

W. C. KEETTEL AND H. B. ELKINS: *Am. J. Obst. & Gynec.*, 71: 553, 1956.

In 247 patients, cul-de-sac aspirations at the time of dilatation and curettage revealed no abnormal cells. In 275 patients, peritoneal washings at laparotomy revealed abnormal cells in 17 instances. Fourteen had ovarian cancer, two extensive uterine malignancy, and one was a false positive. Five patients with cystadenocarcinoma showed no clinical evidence of spread, yet abnormal cells were found in the peritoneal washings.

Patients with Stage I and IIA ovarian carcinoma are now treated with total abdominal hysterectomy, bilateral salpingo-oophorectomy, use of Au^{198}. The remainder of the patients with ovarian carcinoma are treated with surgery, external irradiation and radioactive gold when feasible. The majority of patients tolerate Au^{198} with minimal complications. Colloidal gold is of value in controlling formation of ascitic fluid in certain patients.

Sufficient time has not elapsed to evaluate five-year survival rates but results seem encouraging.

ROSS MITCHELL

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THERAPEUTICS

Isoniazid, Streptomycin and Para-Aminosalicylic Acid Compared as Two-Drug Regimens in the Treatment of Pulmonary Tuberculosis Among Previously Untreated Patients.

III. An Account of the Cooperative Investigation of the Veterans Administration, Army and Navy, August 1952 to September 1954.

W. B. TUCKER AND D. G. LIVINGS: *Am. Rev. Tuberc.*, 72: 756, 1955.

Isoniazid, streptomycin, and para-aminosalicylic acid (PAS) were compared as two-drug regimens in the treatment of bacteriologically proved pulmonary tuberculosis. A total of 2,187 patients without prior drug therapy were assigned at random to one of the following three regimens: isoniazid, 300 mg. per day, plus 12 g. of PAS per day; isoniazid, 300 mg. daily, plus 1 g. of streptomycin twice weekly; streptomycin, 1 g. twice weekly, plus 12 g. of PAS per day. Analysis of factors characterizing the patients and their disease showed the resulting three treatment groups to be highly comparable.

The best results, with respect to the criteria reversal of infectiousness ("conversion by culture"), favourable roentgenographic change, and cavity closure, *were obtained with the isoniazid-PAS regimen*, the poorest, with streptomycin-PAS. The results with isoniazid daily plus streptomycin twice weekly were slightly less good than those with isoniazid-PAS administered daily. The more advanced the disease and the greater the cavitary component, the more marked was this differentiation.

Analysis of the results according to the criterion of significant roentgenographic improvement (moderate plus marked degrees of improvement) showed it to be poorly correlated with the other criteria listed, especially with respect to the stage of the disease and the cavitary component of more advanced disease. It is concluded, therefore, that the criterion of significant roentgenographic improvement is of restricted value in such studies and that other more objective measures are more reliable.

As regards variables other than the drugs employed, race and age do not appear to be clearly associated with outcome; results are less satisfactory the more advanced the disease and the larger its cavitary component at the start of therapy; bilateral involvement responds less well than unilateral. It has not been possible to analyze the relative influence of differing durations of therapy. The vast majority of patients were treated for more than 12 months, but the evidence continues to suggest that 12 months of therapy is the minimum advisable and that more may be advisable in most patients.

When either isoniazid or PAS is administered daily as the companion to streptomycin twice weekly, rates for the emergence of streptomycin-resistant strains of tubercle bacilli are comparable. When PAS daily is compared with streptomycin twice weekly as the companion for daily isoniazid, however, the rates for the emergence of drug-resistant organisms (resistant *in vitro* to isoniazid concentrations of 5 μg. per ml.) are significantly higher for the daily isoniazid and twice-weekly streptomycin regimen. The clinical significance of this finding, however, is not clearly established.

Investigations of the Veterans Administration, Army and Navy, of the United States Public Health Service group, and of the British Medical Research Council trials were compared; there is good agreement that regimens which employ isoniazid with either streptomycin or PAS are approximately equally effective, but that streptomycin twice weekly as the companion for isoniazid is slightly less effective than isoniazid-PAS. M.R.C. trials indicate that the combination of daily isoniazid and daily streptomycin gives consistently the best results.

The final decision on antimicrobial therapy to be prescribed in practice will depend on variations of the disease and on other factors not included in the large-scale British and United States co-operative studies.

S. J. SHANE

Present Status of Anticoagulant Therapy in the Treatment of Myocardial Infarction; The Use and Misuse of Anticoagulants; An Evaluation of New Anticoagulants, Their Indications and Dosage.

I. S. WRIGHT: *Ann. Int. Med.*, 43: 942, 1955.

Anticoagulants in the treatment of myocardial infarction are now being used in many leading centres throughout the civilized world. They are also being used in many smaller communities with suitable facilities. Some workers believe that anticoagulants should be used only for severe cases, or for those who have already suffered thromboembolic complications, but the trend in the leading clinics with large experience with this form of therapy is in favour of using anticoagulants in all cases of myocardial infarction unless there are contraindications.

Long-term anticoagulant therapy after one or more myocardial infarctions appears to give the patient a better prognosis. However, further study and analysis are essential before this position can be accepted as absolutely conclusive.

Major factors responsible for the misuse of anticoagulants include: (1) self-medication without prothrombin tests; (2) medication under physician's directions but without correct control; (3) administration of anticoagulants in the face of contraindications; (4) withholding of anticoagulant therapy in the presence of definite indications; (5) excessive dosage; and (6) inadequate dosage.

Accumulated experience with these drugs has reduced the relative incidence of serious hæmorrhage. Serious hæmorrhage is rare in mildly and moderately ill patients. The availability of vitamin K_1 has increased safety.

New coumarin and phenylindanedione derivatives have been introduced for clinical use. Their rate and duration of action vary, but their effectiveness depends fundamentally on their action on prothrombin and factor VII activity. The value of these drugs does not appear to be very different, and the *facility with which the physician uses them probably constitutes the most important single factor in securing therapeutic results with safety.*

Heparin remains the only drug of its type suitable for clinical use. The so-called anticoagulants with enzymatic properties are thus far in an experimental phase and are not recommended for general use in man, pending much more comprehensive and critical evaluation.

S. J. SHANE

Effect of Cortisone in Treatment of Tuberculous Meningitis.

E. L. KENDIG, JR., S. H. CHOY AND W. H. JOHNSON: *Am. Rev. Tuberc.*, 73: 99, 1956.

Although it is generally agreed that cortisone exerts a deleterious effect on pulmonary tuberculosis, there is some evidence that it may be of value in the treatment of tuberculous meningitis. It has been shown that, when used in conjunction with antimicrobial therapy, this hormone may be helpful in preventing cerebrospinal fluid block, the most dreaded complication of that disease. In this paper the results of the addition of cortisone to the therapeutic regimen of two cases of tuberculous meningitis are reported, and the extreme results of such treatment are presented.

One of the cases is considered to demonstrate a failure of cortisone with respect to the meningitis. Moreover, the pulmonary lesion progressed to cavity formation during the antimicrobial and hormonal therapy. The authors state that, under ordinary conditions, cortisone would not have been used when a pulmonary lesion was known to exist; but the patient was moribund and there appeared to be little to lose. Despite the fact that the writers class this as a treatment failure, they also note that the patient showed temporary improvement on cortisone therapy, that there were no signs of active tuberculous disease in the lungs at autopsy, and

that spinal fluid examined three days before death was normal. It appears clear that the tuberculous meningitis was under control at the time of death.

The other case showed every clinical sign of cerebrospinal fluid obstruction, and on cortisone therapy the evidences of "block" disappeared. The authors conclude that cortisone may be of value in the prevention of cerebrospinal fluid block associated with tuberculous meningitis. They feel that extreme caution is indicated whenever pulmonary tuberculosis is known to coexist.

S. J. SHANE

Hinconstarch in the Treatment of Pulmonary Tuberculosis.

V. C. BARRY *et al.*: *Am. Rev. Tuberc.*, 73: 219, 1956.

Hinconstarch is a polymer prepared from periodate-oxidized potato starch by condensation with equimolar proportions of isoniazid and p-aminobenzalthiosemicarbazone. In a previous study this preparation showed high activity in mice and guinea pigs infected with tubercle bacilli susceptible or resistant to isoniazid, and its toxicity for mice was very low. In the light of these facts, it was considered that hinconstarch deserved investigation in human tuberculosis.

The pilot trial reported here was designed to examine the therapeutic efficiency of hinconstarch in pulmonary tuberculosis, to establish the appropriate dosage, and to study the emergence of isoniazid-resistant bacilli in hinconstarch-treated patients.

Twelve patients with pulmonary tuberculosis were studied for three months, and the drug was given orally in daily doses ranging from 1.2 to 1.6 g. The patients had a variety of clinical types of pulmonary tuberculosis, and the results after three months appeared at least as good as those obtained with other regimens.

The roentgenographic changes were noteworthy, improvement being observed in all cases. Of 9 patients with cavities, these cavities were no longer present in 5, and possibly in 6 patients at the end of the three-month period. In 1 patient all abnormalities had completely cleared roentgenographically at the end of the study period.

As judged by the results of sputum culture for tubercle bacilli, 10 of the 12 patients ceased to be infective. In 2 patients, tubercle bacilli of decreased susceptibility to isoniazid emerged, probably because unnecessary caution was used in the dosage at the onset. The authors feel, however, that an effective dose has now been established, and isoniazid resistance will not be an early or prominent feature of future cases. No undesirable side-effects were noted.

The absence of toxic effects, the therapeutic efficiency, particularly in cavernous disease, and the ease of administration of this tasteless drug, suggest strongly that hinconstarch should have a definite place in the antimicrobial therapy of tuberculosis.

S. J. SHANE

PUBLIC HEALTH

Surveillance of Poliomyelitis in the United States in 1955.

A. D. LANGMUIR, N. NATHANSON AND W. J. HALL: *Am. J. Pub. Health*, 46: 75, 1956.

This article is an evaluation report on the Cutter and Wyeth vaccine incidents which followed the release of the Salk vaccine for commercial use last spring.

The authors, who are members of the National Poliomyelitis Surveillance Program Committee of the U.S. Public Health Service, point out that of the 204 associated cases traced to the vaccine produced by Cutter one-third (79) occurred in vaccinated individuals with an incubation period ranging from 4-14 days; one-half (105) were among family contacts with incubation of 8-28 days; and approximately 17% were community contacts. Three-fourths of the cases were paralytic, and the case fatality rate was 5%. Slightly more than 68% of the cases were in California and Idaho. The other cases were scattered among 22 states and the Territory of Hawaii. One of the chief characteristics of cases due to this vaccine was the correlation of site of first paralysis with the site of inoculation.

Cases were first reported the last of April. On May 7 the Surgeon General suspended the nation-wide vaccination program and began exhaustive tests. Health officials were alerted. Late in May several cases were reported in Pennsylvania and Maryland; these were traced to the Wyeth Laboratories.

Beginning the middle of May and continuing to the present, all lots of vaccine have been released under revised safety standards. Since this time there has been no trouble. However, the committee continues its work of epidemiological evaluation with all states and territories reporting cases among vaccinated children.

Suspension of the program, after some 4,000,000 children in the first and second grades had been inoculated at least once, gave the committee an unusual opportunity to draw some conclusions as to the efficacy of the vaccine. In New York State alone it was ascertained that the proportion of paralytic poliomyelitis was five times higher in unvaccinated children than in those vaccinated.

Since there are many possible sources of error in these preliminary reports, an age distribution analysis study was designed to give a more accurate picture. Comparisons made between the 1952 paralytic attack rate and that of 1955 (for ages 7 and 8) show a relatively sharp lowering of the rate for these ages in 1955.

ISABEL M. LAUDER

Poliomyelitis Vaccine in the Fall of 1955.

J. E. SALK: *Am. J. Pub. Health*, 46: 1, 1956.

The author undertakes to answer the question "How does one ascertain vaccine safety?" He states that the difficulty encountered in the spring of 1955 was due to technique and not to theory and method.

Dr. Salk bases this on the fact that not all manufacturers experienced the same degree of inconsistency; in fact, the experience of most did coincide with what was expected theoretically. Further support of this view was derived from (1) analysis of manufacturing practices and experiences; (2) exhaustive tests upon fluids from the manufacturing laboratories; (3) the effects upon the record of consistency, when specific attention was directed to certain technical details.

The analysis of these facts suggested the likelihood that the virus incorporated in the solid phase of the vaccine and out of contact with the inactivating agent (i.e. formalin) was causing the trouble. In the process of manufacture, after the initial filtration (in some cases), which supposedly removed from the medium solid particles which could protect the virus, the vaccine was allowed to stand weeks and even months before application of formalin. During this time precipitates formed and settled, incorporating and protecting live virus. When tests were made of the liquid phase of the vaccine, a negative result was recorded. When these vaccines were agitated and pooled with others, the sediment would again release the live virus. This gave rise to the idea that the virus was "reactivated". It was ascertained that the filtered virus should not be allowed to stand longer than 72 hours before the formalin treatment.

Dr. Salk relates the complex methods of testing now used for assuring vaccine safety. A defence is made of the use of the Mahoney strain (most virulent) during initial trials. Deliberate consideration was given before this strain was used, and pre-existing knowledge guided the decision; for instance, the fact that a vaccine made from the virulent phase I pertussis organisms is more effective than vaccine made from less virulent types. Other immunological examples also exist.

It was feared that if the Mahoney strain had not been used the basic proof that a killed-virus vaccine can

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actually produce immunity would not be obtained. In fact, there are still those who question this, and believe that the only reason for immunity is that traces of live virus remain in the vaccine, or that virus is reactivated after injection. There has been no proof of these hypotheses; the weight of evidence is to the contrary.

Dr. Salk concludes by stating that the present regimen of inoculations—i.e., two doses, spaced not less than two weeks apart and preferably four to six weeks apart, with a third dose not less than seven months after the second, should be continued. The study of booster doses for pre-school children and infants, as well as research on perfection of the vaccine, is continuing.

ISABEL M. LAUDER

INDUSTRIAL MEDICINE

Air Pollution—Some Epidemiologic Aspects.

W. M. GAFAFER: *Am. Indust. Hyg. A. Quart.*, 16: 196, 1955.

Experience in the Meuse River valley, Donora, Poza Rica, and Greater London leaves no doubt that polluted air can kill. It is suggested that the dictum of factory epidemiology—that all pollutants be considered potentially hazardous until proved otherwise—might be extended to work in community air pollution. Moreover the need is not restricted to a study of the temporary but spectacular health effects of air pollution; it includes a study of the total air pollution problem. Interest must include the effects in inter-epidemic periods.

This article first refers to some implications of the epidemiological method of study. All relevant factors should be taken into account—those related to the individuals comprising the exposed population and those related to the environment. It must be remembered too that there is no known disease entity or specific condition associated with air pollution. In this respect the investigator faces a situation diametrically opposed to the one presented in classic epidemiology.

The author then discusses some results derived from the following studies: the London fog of 1952, and the current Detroit-Windsor and California studies. These indicate the present status of the methodology employed in assessing health effects.

Details are given of each study and the way in which factors believed related to the episode were investigated. The London study was based primarily on death certificates. In the currently conducted study in the Detroit-Windsor area, the methodology of the sickness-survey is used. Households in high and low air pollution areas are visited periodically by trained enumerators who collect many data. In California comparisons have been made of certain characteristics of illness suffered in Los Angeles during smog and non-smog periods.

Consideration of these three investigations indicates that closer attention should be given to the quantitative aspects of the exposure of the population to the pollutants. Moreover the absence of correlation between health effects and air pollution as noted in some of the preliminary studies may mean merely that the factors chosen as relevant were only remotely related to the problem, or that the methods of measurement were somewhat deficient.

It is suggested that in addition to continuing sickness-surveys and various kinds of laboratory and clinical work, a long-term study of the possible time changes in the correlation of sickness and mortality with atmospheric conditions might be carried out in some carefully chosen geographic area. Only concerted action on all fronts can lead eventually to an economically and socially sound air pollution program.

MARGARET H. WILTON

OBITUARIES

DR. MAXWELL BOWMAN, 60, Director of Medical Services for the Province of Manitoba, died on April 26 at his desk in the Legislative Building, Winnipeg. He was born in Miami, Man., and graduated with the degree of M.D. from the Medical Faculty of the University of Manitoba in 1920. He practised in Sperling until 1928, when he became a municipal doctor at Clanwilliam. In 1935 he attended the University of Toronto and obtained the Diploma in Public Health.

In 1939 Dr. Bowman joined the staff of the Provincial Government as epidemiologist, three years later he became Professor of Social and Preventive Medicine in the University of Manitoba, retiring in 1952. In 1955 he was appointed Fellow of the American Board of Preventive Medicine.

During the poliomyelitis epidemic of 1953 Dr. Bowman worked tirelessly and showed his medical and executive ability. When the Salk vaccine became available, he arranged for its orderly distribution to the children of the province.

He is survived by his widow; four sons, of whom John and William are able pædiatricians; a daughter, and ten grandchildren.

An editorial in the *Winnipeg Free Press* mentioned his devoted service in preventive medicine and the pure joy he must have felt when the success of the vaccine apparently made impossible the repetition of another epidemic of poliomyelitis.

DR. DAVID MICHAEL CLAPIN, a medical officer in the R.C.A.F., died suddenly at St. Johns, Que., in April, at the age of 30. He was born in Ottawa and graduated from the University of Ottawa in 1951. He had served with the R.C.A.F. in Western Canada and in the Yukon.

Dr. Clapin is survived by his widow, three sons and a daughter.

DR. HOWARD C. DIXON of Calgary died in hospital on May 8.

Dr. Dixon was born at Maple Creek, Sask. in 1885. He received his Bachelor of Arts degree from Wesley College, Winnipeg and his M.D., C.M. from McGill University in 1913. He served overseas with the Canadian Army Medical Corps for four years during the first World War. In 1915 he married Beatrice L. Armitage, who was serving overseas as a nurse. In 1920 Dr. Dixon located in Medicine Hat, Alta., where he continued to practise until retiring to Calgary in 1954.

An elder and former clerk of the Session of the Fifth Avenue United Church in Medicine Hat, Dr. Dixon was also past president of the Medicine Hat Kiwanis Club; a member of the Masonic Lodge at Medicine Hat and a member of the Medicine Hat School Board for many years as well as one of the original members of Phi Kappi Pi Fraternity, Alpha Beta Gamma Chapter; and a member of the Maple Creek Old Timers Association. In Calgary he was a member of the Downtown Kiwanis Club and a member of Riverview United Church.

He is survived by his widow, a daughter and three sons.

DR. ROBERT EDMUND JOHNSTON, 72, a general practitioner of Toronto, died on April 28. Dr. Johnston was born in Moore Township, near Sarnia, Ont., and graduated from the University of Toronto in 1910. During World War I, he transferred from the Canadian Army and served with the Royal Army Medical Corps in France and Egypt. At the close of the war he commanded Spadina Military Hospital. Later, he was associated with Toronto Western Hospital.

Dr. Johnston is survived by his widow, a daughter and a son.

DR. JOHN HEPBURN

AN APPRECIATION

Dr. John Hepburn was admired, respected and loved by all who came under his influence and those who had even brief contact with him were always influenced by his great, strong, definite, sometimes a little frightening but always kindly personality. His life was an unusually interesting one and his whole being reflected his varied experiences.

He was born in Glasgow on December 27, 1888 and grew up in the Orkney Islands where his father was principal of a high school. As a boy he often watched the ships of the British Navy in Scapa Flow near by. Having a keen, clear mind, naturally strong and broad interests and great ability to concentrate and remember, he could not help being a good student. He entered the Edinburgh University medical school at 16 years of age and began immediately the study of patients along with his premedical sciences. A misunderstanding with the famous Professor Cunningham and a subsequent heated discussion about it with his father led the impulsive high-spirited student to give up his medical course after the second year and come to Canada to make his own way, refusing help from home. One could tell of numerous interesting, amusing and exciting incidents as he went from job to job, always working well whether with a pick and shovel as the Canadian Northern Railway was being put through the mountains or as a teamster or in an explosives factory or in other occupations. He worked and played and read and discussed with zest. He was interested in the people and the places, the sport and the natural phenomena and all the activities of his environment; and he always won the affection and respect of his associates. Once, in the depression of 1911, he walked the streets of Vancouver without food and slept in parks, seeking work and finding none for two days. On the morning of the third day he was beginning to feel that he would be obliged either to beg or to steal, each being about equally repulsive to him, when a man driving a wagon offered him a job as a teamster. He had never put harness on a horse before, yet within three months his employer offered to take him into partnership.

When war broke out in 1914 he joined the Seaforth Highlanders and served overseas till severely wounded early in 1918. He was sent back to Canada and discharged. Dr. Hermann Robertson, the medical officer who boarded him out of the Army in Toronto, suggested that he should resume his medical studies interrupted twelve years before. At first he would not consider it: he could not afford it; he was married. Couldn't his parents help him? Of course they could but he would not ask them. Dr. Robertson would ask them. He would not hear of that. But he finally agreed to accept the one year's vocational training offered by the Government and wrote about it to his father, who cabled back at once offering the necessary funds. He began to review anatomy, physiology and biochemistry in the summer of 1918 and entered the University of Toronto class of 1921 in the same fall. He headed the year in the next final and all subsequent examinations and began a brilliant and colourful professional career.

After a year spent in physiology with Professor Macleod, while Banting and Best were working on insulin, he served a junior internship at the Toronto General Hospital. While on the medical wards he played an active part in early studies of the clinical use of insulin, frequently taking blood from patients for blood sugar determinations at one or two hour intervals day and night.

Professor Duncan Graham had early recognized his great qualities of mind and character and took him on the teaching staff in 1923, just two years after his graduation. Dr. Hepburn at once acquired a great reputation both as a lecturer and as a clinical teacher. He was clear and incisive, and he knew how to stress important factors and leave out details unnecessary for his students at their stage. His wit was as penetrating as his intellect and many students who tried to evade his very direct questions smarted under his quips. Those fortunate enough to be in his clinics often said that, even when he taught physical examination only, they learned more medicine from him than from any other teacher in the whole course.

He always remained conversant with the broad field of medicine and had an intensely practical knowledge of patients' symptoms and ills. As time went on, however, he paid greater attention to cardiology. Finally he restricted his private practice (but never his interest and teaching) almost entirely to that field. He remained in the forefront of his growing specialty and became favourably known throughout our Western world as a leader in this work. He took part in many investigations of which the most noteworthy was the recognition, with his great friend the late Dr. Harold Rykert, of the electrocardiographic changes indicative of severe left ventricular strain.

In dealing with sick people he had great ability to recognize essential factors quickly and to make up his mind at once on the proper action to be taken. No effort on his part was too great for the patient who needed help, and he instinctively knew how to give tremendous support.

He had a remarkably forceful personality which made him a dominant figure; he was vivid, virile, full of vigour and interest; he put his whole being into whatever he did whether it was studying the precise use of words, reading, playing bridge, golfing, fishing, or working. He made strong and enduring friendships. In particular he was wonderfully fond of children, whether sick or well, and they all adored him.

He was steadily advanced in positions of influence and responsibility, becoming senior cardiologist to the Toronto General Hospital, Associate Professor of Medicine at the University of Toronto, President of the Canadian Heart Association, Canadian representative on the Inter-American Society of Cardiology and for two years President of the Royal College of Physicians and Surgeons of Canada.

In recent years his friends saw with regret that his health was failing. A severe gluteal intermittent claudication and a recurrently active thrombophlebitis forced him to give up the physical activities which he loved. His interest never flagged, however, and he continued to work although for shorter hours till the day before his death. He would read a book a day and, to the wonder of his friends, would remember well what he read. He continued to play bridge regularly and to take an active part in medical discussions. He carried on with heavy Royal College work while often tired out and when it was apparent that he was failing slowly.

On the day of his death, March 30, he began to suffer severe pain indicative to him of a perforating arteriosclerotic aneurysm. Knowing that his illness was serious, he went to the operating room for an attempted aorta transplant, apparently calm and joking about casual matters as he had always done. The hæmorrhage was too extensive and he died before it was possible to help him.

His friends will always remember with admiration his great fortitude, his ability to endure quietly, his strong intellect and competence, his keen perception and robust humour, his great kindness and affection and his capability in all activities of life. They will remember his lack of vanity and arrogance, his hatred of sham and pomposity and humbug, and his pride of rectitude and fair dealing which would not let him stoop.

He is survived by his widow who had shared his trials and anxieties and joys from the days before the first World War, by his daughter Mary (Mrs. John MacDougall) and by his year-old grandson, John Scott MacDougall, whose presence filled the last year of his life with interest and joy.

R. F. FARQUHARSON

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FORTHCOMING MEETINGS

CANADA

CANADIAN PÆDIATRIC SOCIETY, Delawana Inn, Honey Harbour, Ontario. (President, Dr. J. H. Ebbs, The Hospital for Sick Children, 555 University Avenue, Toronto 2, Ont.) June 4-6, 1956.

CANADIAN OTOLARYNGOLOGICAL SOCIETY, Château Frontenac, Quebec, Que. (Dr. G. Arnold Henry, Secretary, 328 Medical Arts Bldg., 170 St. George St., Toronto 5, Ont.) June 6-7, 1956.

CANADIAN OPHTHALMOLOGICAL SOCIETY, 19th Annual Meeting, Château Frontenac, Quebec, Que. (Dr. R. G. C. Kelly, 90 St. Clair Avenue West, Toronto 7, Ont.) June 7-9, 1956.

CANADIAN UROLOGICAL ASSOCIATION, 12th Annual Meeting, Alpine Inn, Ste. Adèle, Quebec. (Dr. D. Swartz, Secretary, C.U.A., 332 Medical Arts Building, Winnipeg 1, Man.) June 7-9, 1956.

SOCIETY OF OBSTETRICIANS AND GYNÆCOLOGISTS OF CANADA—1956 Annual Meeting, Manoir Richelieu, Murray Bay, Quebec. (Dr. F. P. McInnis, Secretary, Society of Obstetricians and Gynæcologists of Canada, 1230 Avenue Road, Toronto, Ont.) June 8-10, 1956.

CANADIAN MEDICAL ASSOCIATION, 89th Annual Meeting, Ecole de Commerce, Quebec, Que. (Dr. A. D. Kelly, General Secretary, Canadian Medical Association, 150 St. George Street, Toronto 5, Ont.) June 11-15, 1956.

CANADIAN RHEUMATISM ASSOCIATION, Annual Meeting, Room 312, Ecole de Commerce, Quebec, Que. (Dr. J. B. Frain, Secretary-Treasurer, Winnipeg Clinic Building, Winnipeg 1, Man.) June 14-15, 1956.

CANADIAN DERMATOLOGICAL ASSOCIATION, Quebec, Que. (Secretary, C.D.A., 429 Medical Arts Building, Winnipeg, Man.) June 14-16, 1956.

CANADIAN ANÆSTHETISTS' SOCIETY, Mont Tremblant Lodge, Mont Tremblant, Quebec. (Dr. R. A. Gordon, Secretary-Treasurer, C.A.S., 516 Medical Arts Building, 170 St. George St., Toronto 5, Ont.) June 18-20, 1956.

UNITED STATES

THIRD NATIONAL CANCER CONFERENCE, Sheraton-Cadillac Hotel, Detroit, Michigan. (National Cancer Conferences Coordinator, American Cancer Society, 521 West 57 Street, New York 19, N.Y.) June 4-6, 1956.

AMERICAN COLLEGE OF CHEST PHYSICIANS, 22nd Annual Meeting, Hotel Sherman, Chicago, Illinois. (Executive Offices, A.C.C.P., 112 East Chestnut Street, Chicago 11, Ill.) June 6-10, 1956.

AMERICAN MEDICAL ASSOCIATION, Annual Meeting, Chicago, Illinois. (Dr. George F. Lull, 535 North Dearborn Street, Chicago 10, Ill.) June 11-15, 1956.

AMERICAN ELECTROENCEPHALOGRAPHIC SOCIETY, 10th Annual Meeting, Claridge Hotel, Atlantic City, New Jersey. (Dr. W. T. Liberson, Secretary, A.E.S., V.A. Hospital, Northampton, Mass.) June 15-17, 1956.

WORLD CONFEDERATION FOR PHYSICAL THERAPY, Second International Congress, New York, N.Y. (Canadian Physiotherapy Association, 8 Bedford Road, Toronto 5, Ont.) June 17-23, 1956.

SOCIETY OF NUCLEAR MEDICINE, Hotel Utah, Salt Lake City, Utah. (Secretary, Dr. R. G. Moffat, 2656 Heather Street, Vancouver 9, B.C., Canada.) June 21-23, 1956.

INTERNATIONAL CONGRESS OF HEMATOLOGY, Boston, Massachusetts. (International Society of Hematology, New England Center Hospital, Harrison Avenue at Bennett Street, Boston 11, Mass.) August 26-September 1, 1956.

SIXTH INTERNATIONAL CONGRESS OF BLOOD TRANSFUSION, Boston, Massachusetts. (Professor I. S. Ravdin, President, New England Medical Center, Harrison Avenue, Boston 11, Mass.) August 29-September 2, 1956.

INTERNATIONAL COLLEGE OF SURGEONS, 10th International Congress, Chicago, Illinois. (Dr. Max Thorek, 1516 Lake Shore Drive, Chicago, Ill.) September 9-13, 1956.

INTERNATIONAL CONGRESS OF CLINICAL CHEMISTRY, New York, N.Y. (Mr. J. C. Reinhold, 711 Maloney Building, Hospital of the University of Pennsylvania, Philadelphia 4, Pa.) September 9-14, 1956.

OTHER COUNTRIES

THIRD INTERNATIONAL SCIENTIFIC CONFERENCE ON RHEUMATISM, Aix-les-Bains, France. (M. Graber-Duvernay, 6 rue de Liége, Aix-les-Bains.) June 28-July 1, 1956.

BRITISH MEDICAL ASSOCIATION, Annual Meeting, Brighton, England. (The Secretary, B.M.A. House, Tavistock Square, London, W.C. 1, England.) July 5-13, 1956.

FIFTH INTERNATIONAL CONGRESS ON GASTROENTEROLOGY, London, England. (Mr. Hermon Taylor, 14 Upper Harley Street, London W.1.) July 18-21, 1956.

INTERNATIONAL SYMPOSIUM ON MEDICAL-SOCIAL ASPECTS OF SENILE NERVOUS DISEASES, Venice, Italy. (Secretariat, International Association of Gerontology, Viale Morgagni 85, Florence, Italy.) July 20-21, 1956.

SIXTH INTERNATIONAL PÆDIATRIC CONGRESS, Copenhagen, Denmark. (Dr. J. Vesterdal, Domus Medica, Kristianiagade, Copenhagen.) July 22-27, 1956.

EIGHTH INTERNATIONAL CONGRESS OF RADIOLOGY, Mexico City, Mexico. (Secretariat, I.C.R., Calle del Oro, 15, Mexico, D.F.) July 22-28, 1956.

20TH INTERNATIONAL PHYSIOLOGY CONGRESS, Brussels, Belgium. (Professor J. Reuse, Faculté de Médecine et de Pharmacie, 115 Boulevard de Waterloo, Brussels.) July 30-August 5, 1956.

FIRST INTERNATIONAL CONGRESS OF HUMAN GENETICS, Copenhagen, Denmark. (The University Institute for Human Genetics, Tagensvej 14, Copenhagen.) August 1-6, 1956.

EIGHTH INTERNATIONAL CONFERENCE OF SOCIAL WORK, Munich, West Germany. (J. R. Hoffer, 345 East 46 Street, New York 17, N.Y.) August 5-10, 1956.

WORLD FEDERATION FOR MENTAL HEALTH, Ninth Annual Meeting, Berlin, West Germany. (The Secretary, W.F.M.H., 19 Manchester Street, London, W. 1, England.) August 12-18, 1956.

FOURTH INTERNATIONAL CONGRESS ON DISEASES OF THE CHEST, Cologne, West Germany. (Dr. Murray Kornfeld, American College of Chest Physicians, 112 Chestnut Street, Chicago 11, Ill.) August 19-23, 1956.

SECOND INTERNATIONAL CONGRESS OF PHYSICAL MEDICINE, Copenhagen, Denmark. Dr. B. Strandberg, Koebnhavns Amts Sygehus i Gentofte, Hellerup, Denmark.) August 20-24, 1956.

FIRST PAN-AMERICAN CONGRESS OF GERONTOLOGY, Mexico City, Mexico. (Dr. Manuel Payno, Academie Mexicana de Gerontologia, Avenue Cuahtemoc no. 10-3, Mexico 7, D.F.) September 5-15, 1956.

EUROPEAN SOCIETY OF CARDIOLOGY, 2nd Congress, Stockholm, Sweden. (Professor K. E. Grewin, Sodersjukhuset, Stockholm.) September 10-14, 1956.

25th INTERNATIONAL CONGRESS AGAINST ALCOHOLISM, Istanbul, Turkey. (Bureau International contre l'Alcoolisme, Case Gare 49, Lausanne, Switzerland.) September 10-15, 1956.

PROVINCIAL NEWS

BRITISH COLUMBIA

Several new federal grants have been made to the University of British Columbia recently. Three of these are directed towards research in mental disease, and will be used under the direction of Dr. William C. Gibson, Professor of Neurological Research in the University of B.C.

The first, of $13,577, will be for research into body metabolism in schizophrenia—this is regarded as quite important, since nearly 23% of admissions to Canadian mental institutions in 1954 were for schizophrenia. The second grant, of $12,271, will be for research into brain structure as this affects the present treatment of the mentally ill. The third grant, of $8,673, will be used for a survey of the causative factors in mental deficiency, and will be carried out at the Woodlands School, New Westminster.

Two more grants go to the University. One, of $2,100, is for studies on the morbidity of both mother and fetus during pregnancy. This will be carried out under the direction of Dr. Alec M. Agnew, head of the Department of Obstetrics and Gynæcology of the University of B.C. Medical Faculty. Dr. F. E. Bryans, also of the department, will undertake research into blood levels of adrenal steroids, especially as these influence resistance to disease, and prenatal fetal mortality rates.

The B.C. Medical Research Institute receives a grant of $7,488 to be used in studies of the incidence of and various causative factors in staphylococcal infections. Dr. A. F. Hardyment of the Pædiatrics Department, Vancouver General Hospital, will direct this most important research.

The Royal Jubilee Hospital of Victoria receives a grant of $10,500 to assist in financing an addition to the psychiatric unit. The total of grants made to this hospital in recent years, over $75,000, has aided in the addition of 40 active beds, eight psychiatric beds, and community health centre work.

At the Annual Meeting of the B.C. Surgical Society held in Victoria in April, Dr. John A. Elliott of Vancouver was elected President, succeeding Dr. W. D. Marshall of Victoria. Dr. John A. Frost, of Vancouver, was elected Vice-president.

The guest speaker at this most successful meeting was Dr. Richard B. Cattell, head of the Lahey Clinic, Boston, Mass.

The Children's Hospital of Vancouver is conducting a travelling clinic this month for the first time in its history. The team will go into the Okanagan, visiting Vernon, Penticton and Kelowna, and will be accompanied by an orthopædic surgeon and pædiatrician.

New hospitals are gradually being built, and existing ones expanded, as the population grows in the different areas of the province. Campbell River is to have a new 56-bed general hospital which will serve a large area of this part of Vancouver Island. New ideas appear in the plans for construction of this hospital, such as the "double corridor" type of ward arrangement, and other methods adopted by the most modern hospitals on this continent, calculated to economize on space and to make administration and nursing easier, with less ground to cover and easier access to patients.

Burnaby, as a rapidly growing municipality, is beginning to expand in all health services. The hospital is greatly overcrowded, and increased accommodation is planned. The Children's Health Centre is running at from 90% to 100% or more of its capacity. These things were emphasized by the Medical Health Officer, Dr. W. F. Sutherland, in his annual report. He urged that a weekly garbage collection and a litter-control program be instituted, and asked for more staff, including a part-time medical man and two additional public-health nurses.

The Nanaimo General Hospital, which for so many years has done yeoman service in that city, with its 100 beds, is to be closed; a new hospital will replace it. The new hospital will have some 200 beds, and is urgently needed in this rapidly growing city. Fifty acres are to be set aside for this purpose. The cost of the new hospital is expected to be in the neighbourhood of two million dollars.

The Annual Report of the Western Society for Rehabilitation shows a very active year of work, with a small deficit of some $540, but, in the words of the President, Gordon T. Southam, "the year was very profitable". Complete nursing and psychological and vocational counselling have been added to the facilities of the Society, and the services of the organization are to be added to further and extended.

The Council of the B.C. College of Physicians and Surgeons announces its new officers, as follows:

President, Dr. R. G. Langston, Vancouver; Vice-president, Dr. W. E. Harrison, Vancouver; Treasurer, Dr. R. Scott-Moncrieff, Victoria; Registrar, Dr. Lynn Gunn.

Plans for the Vancouver Medical Association's Summer School are now completed, and an outstanding program has been arranged. The meeting will be held in Stanley Park Pavilion from June 4-8 inclusive—a unique and most beautiful setting for any gathering. The speakers are all well known as leaders in their respective specialties: Dr. Ian Aird, Professor of Surgery, University of London, England; Dr. Richard TeLinde, Professor of Gynecology, The Johns Hopkins Hospital, Baltimore, Maryland; Dr. Karl Menninger, Professor of Psychiatry, Menninger Sanitarium, Topeka, Kansas; Dr. Mark R. Marshall, Professor of Ophthalmology, University Hospital, Edmonton; Dr. Donald C. Balfour, Assistant Clinical Professor and Director of Research (Gastroenterology), University of Southern California, Los Angeles; and Dr. Russell R. de Alvarez, Professor and Executive Officer, Department of Obstetrics and Gynecology, University of Washington, Seattle.

A full program of entertainment for the ladies has been arranged, including golf, boat-trips, and dances.

St. Paul's Hospital's School of Nurses held its graduating exercises on April 25, and 125 graduates received their certificates and medals at a very delightful ceremony at the Georgia Auditorium. Dr. J. W. Frost, chairman of the Medical Staff of the Hospital, acted as master of ceremonies. His Honour, Mr. Justice Coady, who has for a long time been intimately connected with St. Paul's Hospital, was the guest speaker, and gave the Address to the Graduating Class.

J. H. MacDermot

ALBERTA

The 25th Annual Refresher Course held in Edmonton, April 23-27, was outstanding on two counts. For the first time it was held in conjunction with another gathering, the Sectional Meeting of the American College of Surgeons, and it marked the inauguration of the W. Fulton Gillespie Memorial Lecture which was delivered at a special convocation of the University of Alberta.

Dr. Gillespie, then a lecturer in surgery, was the chief motivating force in the group that announced the first Refresher Course in 1929. His interest in, and contribution to it continued through his appointment to the chair of surgery in 1938 until his death on September 3, 1949.

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The Refresher Courses, which are sponsored jointly by the University of Alberta and the Alberta Division of the Canadian Medical Association, have become increasingly popular through the years, and the present combined meeting produced a new record of over 300 registrants. The excellent list of speakers represented a geographical area extending from Montreal and Boston on the east to Los Angeles and Vancouver on the west.

The W. Fulton Gillespie lecture was delivered at a special convocation of the University of Alberta by Dr. James T. Priestley, Professor of Surgery, Mayo Foundation for Medical Research, Graduate School of the University of Minnesota, who was at the same time awarded the degree of Doctor of Laws, honoris causa, by the University of Alberta. Dr. Priestley paid tribute to Dr. Gillespie and his work and then made a plea for an emphasis on the humanities in medical practice, contrasting the pattern of 50 years ago with that of today.

The 50th Anniversary of the Calgary District Medical Society was celebrated at a banquet in the Palliser Hotel on May 1. Over 300 attended the function, at which one of its members, Dr. E. P. Scarlett, Chancellor of the University of Alberta, was awarded a life membership in the Society.

In his address, Dr. Scarlett traced the development of medicine over the last 50 years and made a plea for the maintenance of medicine's tradition of humanity.

Dr. W. E. Ingram, who represents the Society on the Council of the College of Physicians and Surgeons, reported that the proposed subsidization of M.S.I. by the Alberta Government would probably be delayed two or three years, or until agreement is reached on a Dominion-Provincial level. Dr. Ingram stressed that medicine must keep its own house in order as a measure of defence against government intrusion.

Original charter members of the Calgary Medical Society who were present at the gathering were Drs. L. S. Mackid, H. A. Gibson and George Learmonth.

During the evening Dr. J. V. Follett, the continuing treasurer, was presented with a wrist watch in recognition of his 16 years of service in that capacity. Other officers are Dr. D. L. McNeil, President, Dr. A. A. Dixon, Vice-president and Dr. M. D. Mitchell, Treasurer.

In commenting on "Exercise Jeff", held recently in North Central Alberta, Major General Worthington said it was the best civil defence exercise he had seen anywhere. Other observers were Dr. K. C. Charron and Dr. Gordon Fryer of Ottawa, and Dr. A. D. Kelly of Toronto.

The exercise visualized a major disaster in the City of Edmonton and Ponoka, with assistance from the reserve army, medical units and the auxiliary air force medical services, through provincial headquarters.

The simulated casualties were passed through an advance treatment centre to 23 Medical Company, R.C.A.M.C. Reserve, and from there evacuated by road to Ponoka, and by the Air Force Evacuation Unit to Penhold. At Ponoka the casualties went through a triage centre operated by the Ponoka advance treatment centre, the surgical cases being sent to the Ponoka Municipal Hospital, and the burn and other cases to the Provincial Mental Hospital. The 22 Medical Company Reserve, stationed at Ponoka, provided ambulance service there.

The Ponoka Civil Defence authorities showed a high degree of efficient organization and all the doctors of the community actively participated in the exercise. Observers were high in their commendation of the cooperation in all phases of the scheme.

Dr. M. A. R. Young, President-Elect of the Canadian Medical Association, Alberta Division, in company with Dr. H. Richard of Edmonton, Dr. J. L. Weatherilt of Lamont, Dr. J. D. Wallace of Wainwright and the Provincial Secretary, attended several District meetings. They were in Brooks on Friday, May 11; Lethbridge, Saturday, May 12; Wetaskiwin, Wednesday, May 16; Red Deer, Wednesday, May 23; and Elk Island Park, the Vegreville District meeting, on May 30.

W. B. PARSONS

QUEBEC

The Jewish Hospital of Hope for chronic diseases in Montreal will open a new wing next autumn. This new building will have a modern occupational therapy department and other rehabilitation facilities, an operating department, a larger pharmacy, and auditorium and increased x-ray equipment.

Quite a number of annual reports from our hospitals have been made public during the past month. Most of these indicate that increased government health grants will be necessary if they are to continue an expanding service, particularly for outpatient services and for indigent patients.

Dr. Hugh Birks, medical director of the Royal Edward Laurentian Hospital, Montreal Division, reported record use of the facilities of the dispensary and the branch x-ray clinics. As a result, the number of tuberculosis cases in Montreal under supervision of this hospital has dropped below 6,000 for the first time in five years. Nevertheless, the Montreal Health Department notes that in 1955 there were 1,276 new cases of tuberculosis reported in the city. This emphasizes that the work done by the various antituberculosis agencies must be continued without let-up.

Returning to the Royal Edward Laurentian Hospital, the Laurentian Division provided 106,701 patient-days last year and the Montreal Division 28,322 patient-days. There was a deficit of $1.23 per patient per day in the hospital, representing the difference between what is paid to the hospital for the care of patients under the Quebec Charities Act and what such care actually costs. This free treatment accounted for a deficit of $166,679 last year.

The annual report of the Royal Victoria Hospital in Montreal, presented by Dr. Gilbert Turner, executive director, was similar in tone. He emphasized that the present reimbursement under the Quebec Public Charities Act is $7.50 per day. On the other hand, the average per diem cost of hospitalization in eight representative hospitals in Montreal, both French and English, was $15 in 1955. The same situation holds true in regard to services provided to indigent outpatients in the clinics.

The last general meeting of the Montreal Medico-Chirurgical Society before the annual meeting was held on Friday, April 20 at 8.30 p.m. at the Queen Mary Veterans' Hospital. This was in the nature of a symposium on "Treatment of Advanced Malignant Disease" with Dr. Gordon A. Copping as chairman, and Drs. Jean Bouchard, John D. Palmer and Louis Lowenstein as panel members. The guest speaker of the evening was Dr. Robert Taylor, Executive Director of the National Cancer Institute. He emphasized that the most vital phase of the battle against cancer is research. Therefore, the larger part of the subscribed funds supports investigations into the various aspects of this disease. Then also, the demand for help by indigent cancer patients is increasing. In Canada, the amount of funds devoted to cancer research during the past 10 years has been increased from $10,000 a year to $800,000.

Premier Maurice Duplessis officiated on April 21 with the Minister of National Health and Welfare, Paul Martin, at the opening of the new Salk vaccine production plant of the Institute of Microbiology and Hygiene of the University of Montreal. This plant, at Laval des Rapides, was built with a $650,000 Quebec Government grant, while the Federal Health Department contributed

$242,000 towards the purchase of laboratory equipment. The Institute is under the direction of Dr. Armand Frappier. Other speakers at the ceremony included the Honourable Edouard Asselin, Government Leader in the Legislative Council and president of the Institute of Microbiology, and Quebec Health Minister Albini Paquette. This new laboratory will increase by some 50% the production facilities of the Salk vaccine in Canada. Until now the Connaught Medical Research Laboratories in Toronto were the only Canadian source of the anti-polio vaccine.

The Quebec Deputy Minister of Health, Dr. Jean Grégoire, has announced that his department is planning to give booster polio vaccine shots to over 207,000 children who were inoculated last year. Vaccine will be distributed to the various sectors of the province according to population. Indications are that the Province's vaccination program for 1956 will not be materially delayed this year because of unacceptability of some of the prepared vaccine.

Dr. Marcel Langlois, Quebec City pædiatrician, has been appointed field representative for the Canadian Commission on Hospital Accreditation. He will survey and inspect Canadian hospitals which seek official recognition by the commission. Dr. Langlois is medical director of the Saint François d'Assise Hospital in Quebec City.

Dr. W. H. Cruickshank of Montreal has been appointed public relations director of the Bell Telephone Co. of Canada. Dr. Cruickshank is well known for his work in preventive medicine, industrial health and personnel studies.

A scrutiny of the 1955 report issued by the Montreal Health Department reveals that deaths due to heart disease climbed from 331.5 per 100,000 in 1954 to 344.2. Cancer was responsible for 162 deaths per 100,000, as compared to 164.1 in 1954. In third place were accidents, with 477 deaths last year, 14 more than in 1954. Nephritis caused 327 deaths compared to 427 for the previous year, and pneumonia 226, a drop of 6 in comparison with the former year. Diabetes caused 160 deaths, compared to 177 in 1954, and tuberculosis 145, compared to 156 the previous year. The department also reports that births increased from 26.3 per 100,000 in 1954 to 26.6 in 1955.

On May 9 Premier Maurice Duplessis presided at the official inauguration of the new Jeffrey Hale's Hospital in Quebec City. The province granted $1,000,000 to the hospital and also purchased the old hospital building at a cost of $750,000.

Mr. R. Belhumeur, Administrator of the Jean Talon Hospital in Montreal, kindly brought to the attention of the writer an error in number of beds made in a report on extension in progress at this hospital. Their present capacity is 83 beds and 13 bassinets. On completion of the new wing this coming fall, bed capacity will number 154, with 25 bassinets. A. H. NEUFELD

NEW BRUNSWICK

Dr. A. H. Neufeld, Senior Consultant in Biochemistry to the Department of Veterans' Affairs, visited Saint John late in March. He addressed a large gathering of professional and technical staff at Lancaster D.V.A. Hospital and the following day visited the Provincial Laboratory where his interest was much appreciated by Dr. R. A. H. Mackeen and staff. Dr. Neufeld's editorship of the Canadian Services Medical Journal and his occasional visits bring refreshing news to the maritime periphery of our country from the medical centres farther inland.

Dr. Lachlan MacPherson, Assistant Superintendent of the Saint John Tuberculosis Hospital, has just left for a three-month visit to the United Kingdom as an exchange Canadian scholar to the Canadian Tuberculosis Association and the National Association for the Prevention of Tuberculosis. He will observe and study work being done in various centres specializing in tuberculosis and other chest diseases. A good portion of his visit will be spent at the Brompton Institute of Chest Diseases. In June, Dr. MacPherson has been invited to present a paper in Bristol at the Annual General Meeting of the British Tuberculosis Association. Dr. MacPherson's wife, Dr. Irene Allen MacPherson, will join her husband in Great Britain in June.

At a Clinical Session in the Victoria Public Hospital, Fredericton, doctors were hosts to the physicians of neighbouring counties on April 12. Dr. Denis N. White, Professor of Neurology of Queen's University, Kingston, Ontario, spoke on "The Changing Face of Epilepsy" and Dr. E. Wilson Ewart of Moncton gave a paper on "The Painful Shoulder". Local doctors presented cases for discussion and the visiting speakers led the question-and-answer session.

Dr. William T. Mustard of Toronto addressed the Moncton District Medical Society on April 18 at the City Hospital on the subject of "The Present Status of Pædiatric Heart Surgery". Selected cases of orthopædic and cardiac interest were presented by local physicians and discussed by Dr. Mustard. The following morning Dr. Mustard gave a ward clinic at the same hospital.

This program was repeated at the Saint John General Hospital on April 19 and 20. Dr. Mustard's visit to these two centres was very much appreciated.

The Post-Graduate Department of Dalhousie University and the New Brunswick Medical Society jointly sponsor these regional meetings.

A new million-dollar wing of the Hôtel-Dieu Hospital at Moncton was officially opened by the Most Reverend Norbert Robichaud, Bishop of Moncton, at the middle of April. This new building adds greatly to the many services of this busy hospital.

Dr. J. R. Mayers, Provincial Director of Maternal and Child Health, visited the Boston Lying-In Hospital for a week in April to observe obstetrical procedures.

A. S. KIRKLAND

CANADIAN ARMED SERVICES

The Royal Canadian Navy recently announced the promotion of the following medical officers to the rank of Surgeon Lieutenant Commander:

Surgeon Lieutenant Commander R. S. Dolman, R.C.N., of Victoria, B.C.; Dr. Dolman is serving in the frigate *New Glasgow* in the Pacific Command. Surgeon Lieutenant Commander N. W. Bradford, R.C.N., of Halifax, N.S.; Dr. Bradford was recently appointed to the aircraft carrier *Magnificent* as Flight Surgeon. Surgeon Lieutenant Commander D. J. Kidd, R.C.N., of Halifax, N.S.; Dr. Kidd has completed two years' service in the R.C.N. icebreaker *H.M.C.S. Labrador,* during which time he had extensive experience in the medical problems associated with maritime operations in Arctic waters. He is being appointed to *H.M.C.S. Stadacona,* Halifax, N.S.

Surgeon Lieutenant Commander D. A. Maciver, R.C.N., of Halifax, N.S., is being appointed to *H.M.C.S. Labrador* as Principal Medical Officer.

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The following medical students were recently promoted to Surgeon Lieutenants and are being appointed for duties in R.C.N. Hospitals in June and July on completion of required internship in civilian hospitals: Dr. J. C. Copeman, University of Toronto; Dr. A. S. Dunn, University of Ottawa; Dr. J. B. Jean, Laval University; Dr. A. M. Legare, University of Ottawa; Dr. T. A. H. McCulloch, University of Toronto; Dr. M. C. Patterson, McGill University. These officers had been previously commissioned in the R.C.N. under the Regular Officer Training Plan and the 21-month university subsidization plan.

The Annual Medical Exercise conducted by the Director General of Medical Services (Army) was held at the R.C.A.M.C. School, Camp Borden, during the period March 20 to 23. Senior medical officers of the Canadian Army, Regular and Militia, as well as representatives of other corps and schools, R.C.N., R.C.A.F., D.R.B., Civil Defence and the United States Army Medical Corps, participated. Of particular note was the contribution of Brigadier K. A. Hunter, recently appointed Co-ordinator of the Canadian Forces Medical Council, who was in the process of turning over to Brigadier S. G. U. Shier the appointment of Director General of Medical Services (Army), and that of Major-General S. B. Hayes, the Surgeon General, United States Army, and the presence of Major-General M. L. Brennan, Adjutant-General; Major-General J. M. Rockingham, G.O.C., 1 Canadian Infantry Division; and Major-General S. F. Clark, G.O.C., Central Command, who participated in the discussions.

The exercise consisted largely of a two-day study of field medical arrangements in the light of nuclear warfare, a one-day critical examination of the 600-bed general hospital and a final day devoted to presentations of clinical problems associated with mass casualties.

A special event during the exercise period was the unveiling in the Corps Mess of an oil painting by Mr. Edward Halliday of London, England, of Her Majesty Queen Elizabeth, The Queen Mother, Colonel-in-Chief of the Royal Canadian Army Medical Corps. This portrait has been presented to the R.C.A.M.C. by the Honorary Colonel Commandant Brigadier E. A. McCusker, C.B.E., M.C., E.D., M.D., C.M.

Lt.-Colonel E. H. Ainslie, C.D., M.D., M.Sc., D.A., F.R.C.P.[C.], Commanding Officer and Medical Specialist, Toronto Military Hospital, was promoted to the acting rank of Colonel and appointed Command Medical Officer, Central Command, on March 15. Temporarily he will continue to carry out the duties of Officer Commanding, Toronto Military Hospital, in addition to those of his new appointment. Colonel Ainslie received his M.D. in 1933 and his M.Sc. in 1935 from the University of Western Ontario. Further training followed in internal medicine and anæsthesia and in 1938 he joined the R.C.A.M.C., Permanent Force. He had overseas service from 1940-45 and obtained the English Diploma in Anæsthesia and Canadian certification in this specialty in 1943. Following World War II he served with D.G.M.S. (Army), Ottawa, and later at Montreal Military Hospital. He resumed postgraduate studies and obtained certification in internal medicine and was made a Fellow of the Royal College of Physicians of Canada in 1950. In 1952-53 he was Medical Specialist with the Canadian Forces in the Far East.

Lt.-Colonel J. W. B. Barr, R.C.A.M.C., of the Directorate of Medical Services, Army Headquarters, addressed the New Brunswick Branch, Defence Medical Association of Canada, at Saint John, N.B., on March 9, 1956. In his talk, "Training of the R.C.A.M.C., Past, Present and Future", Colonel Barr stressed the necessity of a very high level of training to deal with the formidable medical problems of any future war.

Lt.-Colonel A. C. Derby, R.C.A.M.C., Surgical Specialist, Kingston Military Hospital, was guest speaker at a meeting of the Nova Scotia Branch, Defence Medical Association of Canada at Halifax, N.S., on April 25, 1956. Colonel Derby spoke on the important subject "The Treatment of Trauma in Mass Casualties".

Third Canadian Field Ambulance, R.C.A.M.C., has been withdrawn from Korea and returned to Canada, leaving a Canadian medical detachment of two medical officers and a small group of other ranks in support of the reduced Commonwealth Force remaining in Korea.

The 27th Annual Meeting of the Aero Medical Association held in Chicago, April 16-18, was attended by Air Commodore A. A. G. Corbet, E.D., C.D., Q.H.P., Director General of Medical Services (Air), Group Captain D.G.M. Nelson, Commanding Officer, Institute of Aviation Medicine, and other R.C.A.F. representatives. Four papers were presented at the meeting by R.C.A.F. medical officers, and in addition a scientific exhibit was arranged by the Institute of Aviation Medicine.

Air Commodore A. A. G. Corbet, E.D., C.D., Q.H.P., Director General Medical Services (Air), was a member of the examiners of the American Board of Preventive Medicine for certification in Aviation Medicine, held in Chicago, April 15, 1956.

Wing Commander W. W. Laughland attended the First International Symposium on Venereal Diseases and the Treponematoses, held in Washington, D.C., from May 28 to June 1, 1956.

Members of the United States Armed Forces Statistical Departments visited Ottawa and Toronto during the month of May for the purpose of meeting with the Inter-Service Medical Sub-Committee on Medical Documentation and Statistics and visiting medical statistics installations of the Canadian services. While in Toronto the group toured the R.C.A.F. Bureau of Medical Statistics and the Institute of Aviation Medicine. Members of the United States group were: Dr. W. V. Charter, Director, Navy Medical Statistics Division; Mr. E. L. Hamilton, Medical Statistics Division, Office of the Surgeon General, U.S. Army; Dr. H. C. Luykx, Chief, Biometrics Division, U.S. Air Force; and Captain H. T. Gagnon (U.S.N.) (M.C.), Deputy to the Assistant Secretary of Defense (Health and Medical).

Group Captain W. R. Franks and Wing Commander J. C. Wickett attended the meeting of the Advisory Group for Aeronautical Research and Development held in Oslo, Norway, and Copenhagen, Denmark, May 7 to 11, 1956. Two papers were presented by Group Captain Franks. Wing Commander Wickett is the Canadian member of the Aeromedical Panel of the Advisory Group for Aeronautical Research and Development.

NATURAL SELECTION AND ABO BLOOD GROUPS

A study in the University of Iowa brings fresh evidence of a relationship between natural selection and ABO blood groups. Among 879 patients with gastric carcinoma there was a significant increase in incidence of type A, whereas in 1,770 patients with peptic ulcer the incidence of type O was significantly increased.—*Science*, 123: 841, 1956.

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BOOK REVIEWS

THE CYTOLOGY AND LIFE-HISTORY OF BACTERIA. K. A. Bisset, Reader in Systematic Bacteriology, University of Birmingham, England. 164 pp. Illust. 2nd ed. E. & S. Livingstone, Ltd., Edinburgh and London; The Macmillan Company of Canada Limited, Toronto, 1955. $4.25.

The second edition of this work has now been published. It covers a variety of interesting aspects of bacterial morphology pertaining to their cytology, with emphasis on the necessity for regarding bacteria as living entities analogous in structure and function to other living cells. Ten separate chapters are devoted to staining techniques, the surface structure of bacteria, their nuclei, reproduction, sexuality, life cycles, macroformations, evolution and genetics. Many controversial topics of academic significance are discussed by the author; where possible, conclusions drawn are supported by his own observations. The text is profusely illustrated in black and white, and it represents an improvement over the first edition.

Fig. 12 is reproduced through courtesy of Dr. A. L. Houwink, and depicts an electron photomicrograph of the crushed cell envelope of *Spirillum* sp. From this it is inferred that the inner layer of the organism is composed of protein material arranged in regular globular pattern. Although the author has refrained from further comment, the reviewer feels that this feature of normal cell architecture should be brought to the attention of virologists engaged in the study of elementary bodies present in certain infected tissues such as lesions of molluscum contagiosum.

In summary, it may be said that Dr. Bisset has successfully assembled and digested much inaccessible information of value to students of biology and bacteriology, all of which he has presented in attractive and readable form.

MODERN TRENDS IN ORTHOPÆDICS. H. Platt, President, Royal College of Surgeons, London. 331 pp. Illust. Butterworth and Company Ltd., Toronto, 1956. $13.00.

In recent reviews we have commented upon the value of monographs and texts of limited scope in contrast to the book which suffers from attempting to cover too much ground. The present volume supports this view. It is the second in the series, and contains 11 chapters, each by a leading British authority, on subjects of current orthopædic interest. A book of this sort is of course of greatest value and interest to the advanced orthopædic surgeon, yet the chapters on peripheral nerve injuries (by Roland Barnes) and on contractures of the hand (by Guy Pulvertaft) will be esteemed by any surgeon interested in trauma. To be of value, a series of this sort should appear on a regular basis, and it is to be hoped that the editor and publishers will see fit to publish on an annual or biennial basis.

ADMINISTRATIVE MEDICINE. Transactions of the Third Conference, October 6, 7 and 8, 1954, Princeton. Edited by G. S. Stevenson, National and International Consultant, National Association for Mental Health, New York. 172 pp. The Josiah Macy, Jr. Foundation, New York, 1955. $3.00.

This report provides a semi-verbatim account of informal discussions between a group from various disciplines, such as public health, hospital administration, nursing, mental hygiene, personnel management and prepayment medical care administration.

From all that was said at this conference, one wonders whether medical training is of any particular use when it comes to administering a hospital or an insurance plan. An interesting point is raised about administration and medicine. The type of person who goes into the health field is motivated by some need—a need within himself—that draws him to that field, and repels him from business and banking. By selection, he tends to end up in the health field because he probably does not like administrative work in any event. It would seem therefore that physicians in administration should be selected positively, because they are really interested in the field, and not negatively, because for various reasons they cannot practise medicine.

This report is interesting and it should be read by those concerned with medical organization and planning.

We should not plan for our physicians a pattern of dull, deathly uniformity. Surely, a place must be kept for those eccentric prima donnas and individualists without whom there can be no progress. Or is 1984 much nearer than we think?

ATLAS DER ELEKTROKARDIOGRAPHIE (Atlas of Electrocardiography). R. Zuckermann, Specialist in Cardiology, former Director of Research at the State Cardiological Institute of Mexico. 500 pp. Illust. Georg Thieme, Leipzig, 1955. 46.80 marks.

After a short, general introductory section in which the unipolar theory is presented, the main body of the book consists of well-chosen electrocardiograms, each of which is elaborately discussed. These comments reflect the author's application of the unipolar theory to clinical interpretation. Many of these contain speculations of the kind familiar to the serious student of electrocardiography in his daily exercises of analyzing and inferring the clinico-pathological significance of electrocardiograms. He uses Ashman's method for determining spatial axes. Such is the fate of "new" books, for at present rapid progress is being made in extending the application of direct methods in spatial vectorcardiography which should soon supersede Ashman's and analogous methods.

An unusual feature appears in the last 30 pages of the book in which electrocardiograms in a variety of animals and insects are shown. These include crawfish, scorpion, migratory locust, fly, butterfly, bee, chicken, quail, kangaroo, lion, bear, elephant and many others. In general these records indicate that the larger the animal the slower the heart rate and the smaller the bird or insect the more rapid the rate.

For those who are interested in the progress of the National Institute of Cardiology in Mexico City there is a bibliography of publications by all members of its staff.

CARDIOVASCULAR INNERVATION. G. A. G. Mitchell, Professor of Anatomy, University of Manchester, England. 356 pp. Illust. E. & S. Livingstone, Ltd., Edinburgh and London; The Macmillan Company of Canada Limited, Toronto, 1956. $9.35.

In the past few years we have seen the appearance of various highly specialized books that have been recognized immediately as important classics in their own narrow fields. With no disrespect to the authors of these books, it has generally been agreed that only the hardiest or desperate reader could do more than look up special points of interest in them when occasion demanded. No one could be expected to read them for pleasure. Professor Mitchell, on the other hand, has given us in *Cardiovascular Innervation* a book that not only promises to be a classic in neurology, but one that is thoroughly readable as well. No physician or surgeon who claims any sort of specialist knowledge in neurology, cardiology, vascular diseases, and anæsthesia can afford not to become familiar with this book.

As Sir Geoffrey Jefferson says in a laudatory foreword, Mitchell has won a reputation for accuracy of observation and this book includes many of his personal observations made over the past 20 years. Moreover, he presents his own work in fair and sensible balance with the works of many others, and the historical considerations, backed by an authoritative list of references, are a valuable feature. The volume itself is beautifully printed, and the many illustrations, with a few exceptions, are first-rate.

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OPERATIVE TECHNIC IN SPECIALTY SURGERY. Edited by W. H. Cole, Professor of Surgery and Head of the Department, University of Illinois College of Medicine, Chicago. 1,100 pp. Illust. 2nd ed. Appleton-Century-Crofts, Inc., New York, 1956. $20.00.

The names of the contributing authors, like that of the editor, are so well known as recognized leaders of American surgical specialties that an authoritative text is sure to result. Here there is a minimum of outdated material and a maximum of accurate detail in descriptions of procedures found most suitable for each lesion.

This volume fulfils well its announced objective as a companion to "Operative Technic in General Surgery". Such chapters as De Bakey's "acute vascular injuries" and "varicose veins and venous thrombosis", Dorsey on chest surgery, surgery, James Barrett Brown and McDowell on the face, mouth, jaws and neck, Greeley's articles on the treatment of fresh wounds and the closure of surface defects, Smithwick on the autonomic nervous system, Spurling on peripheral nerves, and Meigs and Parsons on gynæcological surgery are examples of the fields covered and the kind of contributors Dr. Warren Cole has obtained.

Though many of the procedures discussed may be considered the province of the general surgeon, definitions of that diminishing field vary. Here is an excellent reference work for any surgeon who may find himself about to operate outside his routine range. Especially commendable is the emphasis on the basic principles of trauma and wound healing in the various specialty fields.

THE BILIARY TRACT. J. A. Sterling, Staff Surgeon, Albert Einstein Medical Center. 424 pp. Illust. The Williams and Wilkins Company, Baltimore; Burns & MacEachern, Toronto, 1955. $10.00.

To present a whole picture of the biliary system as a general surgeon needs it is a real accomplishment. Dr. Sterling has done it in a little over 400 pages. The description of anatomy includes variations in the junction of the pancreatic duct and anomalies of the blood supply to the gallbladder. Discussion of pathology includes lesions of the pancreas. Clinical and physiological considerations are concise and readable. Surgical techniques include the management of fluid balance, postoperative complications, the remaining common duct stone and the indications for reoperation. The difficult subject of evaluation of laboratory investigation is fully discussed, as is the radiological aspect including use of Cholegrafin and T-tube cholangiograms. The non-operative management of patients with lesions of the biliary tract is covered including diet, investigation, relief of pain and electrolyte loss.

"The Biliary Tract" will be useful to general practitioners as well as surgeons and radiologists. Its concise and exhaustive qualities make it a valuable reference work and a textbook for graduate students of surgery.

PATHOLOGIC PHYSIOLOGY. W. A. Sodeman, Professor of Medicine, University of Missouri, Columbia. 963 pp. Illust. 2nd ed. W. B. Saunders Company, Philadelphia, 1956. $13.00.

This revised and expanded edition of the well-known text approaches internal medical diseases by analysis of the disturbed physiology behind the signs and symptoms. It does not discuss diseases as such. It includes sections on the genetics of abnormal growth, nutrition, carbohydrate metabolism, water and electrolyte balance, the endocrines, infections, allergy and physical and chemical agents. The circulatory, respiratory, gastrointestinal, urinary, hæmopoietic and nervous systems are covered in great detail.

The 25 authors are well known as investigators and writers, and their contributions are comprehensive and authoritative. This volume can be highly recommended, as was its predecessor.

CANCER OF THE LUNG, PATHOLOGY, DIAGNOSIS AND TREATMENT. M. B. Rosenblatt, Associate Professor of Medicine, New York Medical College, and J. R. Lisa, Director, Pathology Service, New York City Department of Hospitals. 330 pp. Illust. Oxford University Press, New York, 1956. $15.75.

The recent alarming increase in bronchogenic carcinoma is here attributed to improved diagnosis and greater longevity; but even at that, diagnosis has lagged far behind resection technique, and hence most incipient cases still go untreated. Survival rates continue low because of prevailing advanced admission stages. Physical examination should be skilled and thorough, but radiology offers the best diagnostic approach to early tumours. The practitioner should develop a "high index of suspicion". Due attention is here given to symptomatology, to degenerative changes distal to the tumour, and to metastases.

In the chapter on pathology the upper lobe apical region is stressed. Greene's successful heterologous transplantation of human lung cancer is cited. On page 65 appears the dubious statement on lymph vessels that "The bronchial and periarterial channels drain toward the parenchyma." The obsolete term "atrium" is used.

There are eight special contributors besides the two principal authors. Jackson applies bronchoscopy to inspection, biopsy and exfoliative cytology. Papanicolaou and Foot deal with cells from sputum and aspirates. Chamberlain and Daniels discuss surgical therapy and also write on bronchial adenoma. There is a chapter on palliative treatment by Roswit in which, besides roentgen irradiation, including grid and rotational techniques, such modern isotopes as Cobalt 60, radioactive colloidal chromic phosphate and colloidal gold, and chemotherapeutic adjuncts like nitrogen mustard and cortisone are elucidated. Illustrations, particularly from x-rays, are numerous. There is much up-to-date statistical material (Dorn). The book is compact, well documented and eminently practical.

TUBERCULOSIS IN THE ARMY OF THE UNITED STATES IN WORLD WAR II. E. R. Long, Director, Henry Phipps Institute, University of Pennsylvania, Philadelphia, and S. Jablon, Statistician, Follow-up Agency, Division of Medical Sciences, National Research Council, Washington, D.C. 88 pp. Illust. Veterans' Administration, Washington, 1955. $1.50.

This Veterans' Administration Monograph represents part of the program of follow-up studies carried out by the National Research Council in co-operation with the Veterans' Administration, the Army and the Navy. It presents a detailed study of the induction and separation chest x-ray films of approximately 3,000 randomly selected veterans discharged for tuberculosis and 3,000 veterans selected on the same basis who were not discharged for this disease. It brings out a number of facts of significance both for military purposes and for the more general understanding of tuberculosis.

About half of the men discharged for tuberculosis had the disease in radiologically detectable form at induction. The incidence of apparently new disease developing in service was significantly greater in nonwhite than in white men. The peak breakdown was at the low age of 19 to 22 years. The data indicate clearly that tall, thin men develop the disease more frequently than men of other physical types. The reasons for overlooking lesions on induction films were not always evident. The authors conclude from this study that hope for substantial improvement in screening efficiency rests on the use of supplements such as the tuberculin test and a revision of the examination procedure permitting adequate follow-up observation. Failing this, it would appear that the most reliable and practical screen is dual reading followed by a conference on disagreement. An excellent study and report.

(Continued on page 954)

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BRITISH MEDICAL BULLETIN, RECENT RESEARCH ON VITAMINS. Vol. 12, No. 1. 90 pp. Illust. Medical Dept., The British Council, London, 1956. $2.75.

This volume of essays published by the British Council was originally planned by a committee of which the late Sir Edward Mellanby was chairman. He died before the work was completed and it now takes the form of a memorial number to him. As such, it is a fitting tribute to the man who made so many fundamental discoveries in the field of experimental nutrition and who stimulated so much further research.

The essays, most of which take the form of reviews, are contributed by eminent research workers who have themselves written much of the literature under review, and the resulting whole is therefore both authoritative and stimulating. In the first part of the volume the emphasis is mainly upon the vitamins in relation to pathology and physiology, and this is followed by a more detailed account of specific vitamins.

Space does not permit of a discussion of each individual paper, but mention should be made of the article by Professor Best and his colleagues, who describe the discovery of the food factors required for the normal functions of the liver. Professor Witts's clear and concise review on the role of the B vitamins in the blood and the gastrointestinal tract is based on the most recent researches on the subject and is especially concerned with its application to human diseases. Sir Edward Mellanby's own work on vitamins and bone metabolism and his recent studies of the function of vitamin A in tissue cultures are presented in two papers by Professor McCance and Dr. Holman and by Dr. Honor Fell. A stimulating paper by Professor Adrien Albert emphasizes the wider concept of metabolic interactions between vitamins and their antimetabolites, not only in the field of nutrition, but also in combating infectious diseases and even in tumour growth. Professor B. S. Platt acted as scientific editor, and contributes a broad survey on the place of vitamins in human nutrition.

This number of the Bulletin upholds the high standard which we have come to expect of the British Council medical publications. It will be of value primarily to specialists in nutritional and metabolic fields, but it will be of great interest also to clinicians who wish to bring their knowledge of this subject up to date.

NEURAL CONTROL OF THE PITUITARY GLAND. G. W. Harris, Fitzmary Professor of Physiology, Institute of Psychiatry, Maudsley Hospital, London, England. 298 pp. Illust. Edward Arnold Ltd., London; The Macmillan Company of Canada Limited, Toronto, 1955. $5.00.

In this Physiological Society monograph, Dr. Harris presents a masterly survey of present knowledge concerning the inter-relationship between the nervous system and the endocrine glands. He has made many important contributions to this subject in recent years, and his critical assessment of the literature is to be valued highly.

The probable role of the hypophysial-portal circulation in the control of adenohypophysial function by the hypothalamus is defined in the first half of the book. Individual chapters are devoted to the regulation of pituitary gonadotrophin output, and to the control of ACTH secretion. The regulation of thyrotrophic, lactogenic and growth hormones is discussed in one chapter because of the limited knowledge of these substances available at present. Dr. Harris has made a very strong case for the importance of the portal circulation. There remains a group of workers, among whom Zuckerman is the most notable, who believe that some neural influences can be transported through the systemic circulation. However, this does not detract from the importance of Dr. Harris's work.

The hypothalamic-neurohypophysial mechanisms underlying the elaboration and release of vasopressin and oxytocin form the subject of most of the last half of the book. In his own studies of this problem, Dr. Harris made as good use of his remote control technique of hypothalamic and pituitary stimulation as he did in investigating the gonadotrophic function of the adenohypophysis. It is gratifying to Canadian readers to see Professor J. K. W. Ferguson's work on the role of reflex stimulation of the neurohypophysis in the mechanism of labour receive the attention it deserves.

The last chapter reviews briefly the knowledge of how hormones affect behaviour, and emphasizes the phylogenetic differences in the importance of hormones as regulators of sexual behaviour.

This book is recommended as essential for research workers in the field of neuro-endocrinology and graduate students in physiology. Obstetricians interested in a detailed analysis of the mechanism of parturition and lactation, and clinical endocrinologists will find it a stimulating volume that offers a rational basis for many puzzling clinical phenomena.

PSYCHOSOMATICS. M. Hamilton, Senior Lecturer in Psychiatry, University of Leeds, England. 225 pp. Illust. Chapman & Hall Limited, London; British Book Service (Canada) Limited, Toronto, 1955. $3.60.

This comprehensive book was written primarily for the non-specialist reader. It accomplishes its basic purpose of presenting a broad interpretation of psychosomatic medicine in a simple but fairly complete manner. It is surprising to see the volume of detailed information that is compiled in this relatively short book.

A basic understanding of and theories related to psychosomatic disorders are first clearly discussed, with an excellent outline of the foundation of this concept of medicine. Subsequent chapters are devoted to discussion of the psychosomatic interpretation of symptoms and disorders of the various systems of the body. The current theories related to psychosomatic disturbances are presented in a simple fashion. Much of the pertinent literature is reviewed, and the general over-all effect is that of clarity and simplicity.

The author, Dr. Max Hamilton, of the Department of Psychiatry, the University of Leeds, seems to have the faculty of presenting complex subject matter in a form that is both comprehensive and informative. He carefully refers to some of the disputed interpretations, without attempting to be too dogmatic in the choice of this specific or supposedly correct understanding.

This book is of interest to both the student and the practitioner, and is well recommended because of its many excellent qualities.

IMPARTIAL MEDICAL TESTIMONY. A report by a special committee of the Association of the Bar of the City of New York on the Medical Expert Testimony Project. 188 pp. The Macmillan Company, New York and Toronto, 1956. $3.95.

This is a report on the use of independent medical experts in New York City courts. The report is dated December 1, 1954, and covers two years' operation of the experiment. The cases dealt with were limited to personal injury cases, but the authors believe the procedure could be extended to other types of litigation involving medical evidence.

The gist of the experiment was in the appointment by the judge of an independent medical expert. Lists of medical experts who would be available for this work were compiled by the medical societies. Fees of the independent experts were paid from a fund established by the Alfred P. Sloan Foundation and the Ford Motor Company Fund. The experiment has proven successful and has been adopted as a regular part of the court procedure, and the expense has been included in the court budget.

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CURRENT THERAPY, 1956. Edited by H. F. Conn. 632 pp. W. B. Saunders Company, Philadelphia, 1956. $11.00.

This, the eighth edition of the annual series, continues the high standards of conciseness, competence and convenience that have made these books so popular. Comparison with its immediate predecessor shows that no remarkable advances in treatment have been registered in the past year. However, with its authoritative elaboration of the older methods and drugs as well as its introduction of the "new", this book remains "current and choice" for the busy practitioner.

DICTIONAIRE DES TERMES D'ANATOMIE, D'EMBRYOLOGIE, D'HISTOLOGIE (Dictionary of Anatomical, Embryological and Histological Terms). E. Lovasy and E. Veillon. 624 pp. Libraire Maloine, Paris, 1954. 1,300 Fr. fr.

Ever since the days of the great Testut, French anatomy has been noted for the richness of its nomenclature and for the difficulties which this facility for coining names for structures presents to the translator or the foreign anatomist. It is also not unknown for certain French schools to use terms differing from those in use in others. So far there has been no guide in the French language to assist the bewildered student, and the present work will therefore be of great use both to non-French anatomists and others having to cope with French terminology and to French students of the subject.

It has been prepared by the well-known Professor Veillon, who unfortunately did not live to see the book through the press, and by a medical bibliographer of great industry, M. Ernest Lovasy. Much trouble has obviously gone into the preparation of the work, which contains for each entry sufficient definition to identify quite adequately the structure defined. Not only anatomical terms but also terms used in embryology and histology, inseparable from gross anatomy, are listed. The book is recommended as a work of reference to all interested in French anatomy.

ROYAL AIR FORCE MEDICAL SERVICES, Vol. II. Edited by S. C. Rexford-Welch, Squadron Leader, R.A.F. 703 pp. Illust. H. M. Stationery Office, London, 1955. 75/-

This volume, the second coming from the Royal Air Force, narrates the medical story of the nine Home Commands (Bomber, Fighter, Coastal, Transport, Balloon, Army Cooperation, Maintenance, Flying Training and Technical Training) and the three closely allied formations (the Second Tactical Air Force, the R.A.F. Regiment and Number 60 Group). In successive chapters the history and purpose of each Command are briefly outlined. Most of the accounts are narratives describing the medical organization and administration, and a medical commentary on how the system worked in practice. The development of aviation medicine through the war years is covered comprehensively. Many of the principles established in World War II as a result of combating the increasing physical hazards due to advances in aircraft performance are the foundation of aviation medicine today. The chapter on Transport Command presents problems of preventive medicine that are "global". It emphasizes the similarity of difficulties met with in locations as diverse as Iceland and the Azores.

The Balloon Command, like the others, had to adapt to conditions that were recognized as medically undesirable. Army Cooperation Command includes narratives of the training and development of the airborne forces; i.e., the medical aspect of the training of paratroops. As a history compiled relatively close to the events and based largely on reports made by men who were closely associated with events as reported, this volume represents a further valuable contribution to knowledge on this subject. It reflects the highest credit to the medical services of the R.A.F. The whole volume emphasizes that there can be no predetermined boundary to medical responsibility in war. Hence, there cannot be a fixed rigidity to medical thought or organization.

Books Received

Books are acknowledged as received, but in some cases reviews will also be made in later issues.

Bacterial Anatomy. The 6th Symposium of The Society for General Microbiology. Edited by E. T. C. Spooner and B. A. D. Stocker. 360 pp. Illust. Cambridge University Press; The Macmillan Company of Canada, Ltd., 1956. $5.00.

Operative Technic in Specialty Surgery. Edited by W. H. Cole, Professor of Surgery and Head of the Department, University of Illinois College of Medicine, Chicago. 1,100 pp. Ilust. 2nd ed. Appleton-Century-Crofts, Inc., New York, 1956. $20.00.

The Work of WHO 1955. Annual Report of the Director-General to the World Health Assembly and to the United Nations. Official Record of the World Health Organization, No. 67. 241 pp. Illust. World Health Organization, Palais des Nations, Geneva, 1956. $2.00.

Die Chirurgie des Herzens und der Grossen Gefasse (Surgery of the Heart and Large Vessels). E. K. Frey, Director of the Surgical Clinic, University of Munchen, and G. Kuetgens, Assistant, Surgical Clinic, University of Munchen. 444 pp. Illust. Ferdinand Enke Company, Stuttgart, 1956.

Breast Feeding. F. Charlotte Naish. 161 pp. Illust. 2nd ed. Lloyd-Luke (Medical) Books Ltd., London, 1956. 12/6.

The Practice of Psychiatry in General Hospitals. A. E. Bennett, Associate Clinical Professor of Psychiatry, University of California, School of Medicine, San Francisco, E. A. Hargrove, Assistant Professor of Psychiatry, University of North Carolina, School of Medicine, Chapel Hill, and B. Engle, Department of Psychiatry, University of California, School of Medicine, San Francisco, with contributing authors. 178 pp. Illust. University of California Press, Berkeley and Los Angeles, 1956. $4.00.

The Yearbook of Modern Nursing, 1956. A Source Book of Nursing. Edited by M. C. Cowan. 446 pp. Illust. G. P. Putnam's Sons, New York; McAinsh and Co., Ltd., Toronto, 1956.

Essentials of Dermatology. N. Tobias, Dermatologist, St. Louis State Hospital. 651 pp. Illust. 5th ed. J. B. Lippincott Company, Philadelphia and Montreal, 1956. $8.00.

In the Doctor's Office. The Art of being a Medical Assistant. E. J. Parsons, formerly Research Technician, Department of Biochemistry, College of Physicians and Surgeons, Columbia University, New York. 326 pp. Illust. 2nd ed. J. B. Lippincott Company, Philadelphia and Montreal, 1956. $3.95.

The Hamilton General Hospital School of Nursing, 1890-1955. M. F. Campbell. 172 pp. Illust. The Ryerson Press, Toronto, 1956. $4.50.

Harnableitung in den Darm. Uretero-Sigmoidostomie und Darm-Ersatzblasenbildung. (Diversion of the Urine into the Bowel). H. Boeminghaus, Golzheim Clinic, Dusseldorf. 59 pp. Illust. Georg Thieme Company, Stuttgart; Intercontinental Medical Book Corporation, New York, 1956. $3.60.

Proceedings of the Fifth Middle East Medical Assembly, April 22-25, 1955. 564 pp. Illust. The American University of Beirut, 1955.

Physiology and Pathology of Infant Nutrition. L. F. Meyer, Director Emeritus of the Children's Department of Municipal Hospital "Hadassah", Tel Aviv, Israel, and E. Nassau, Chief, Children's Department, Central Hospital of the Workers' Sick Fund, Afulah, Israel. Translated by K. Glaser and S. Glaser. 2nd ed. Revised. 533 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1955. $12.75.

The Laboratory Diagnosis of Coagulation Defects. P. De Nicola, Associate Professor, Department of Internal Medicine, University of Pavia, Italy. 240 pp. Illust. American Lecture Series. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1956. $8.25.

Metabolism, Pharmacology and Therapeutic Uses of Gold Compounds. W. D. Block, Associate Professor of Biological Chemistry, Department of Dermatology, and K. Van Goor, Formerly Instructor, Department of Dermatology, University of Michigan Medical School, Ann Arbor. 76 pp. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1956. $3.00.

Complications of Regional Anæsthesia. D. C. Moore, Director, Department of Anæsthesiology, Mason Clinic, Seattle, Washington. 291 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1955. $11.50.

The Psychosomatic Genesis of Coronary Artery Disease. D. C. Peete, Associate Clinical Professor of Medicine, and Lecturer in the History of Medicine, University of Kansas School of Medicine, Kansas City. 220 pp. Illust. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1955. $8.50.

Subacute Bacterial Endocarditis. A. Kerr, Jr., Assistant Professor of Medicine, Louisiana State University School of Medicine, New Orleans. 343 pp. Illust. American Lecture Series. Charles C Thomas, Springfield, Ill.; The Ryerson Press, Toronto, 1955. $7.25.

The Dental Assistant's Handbook. G. I. West. 2nd ed. 115 pp. Illust. William Heinemann, Ltd., London, 1956. 10/6.

Studies on Expenditure of Energy and Consumption of Food by Miners and Clerks, Fife, Scotland, 1952. R. C. Garry and others. Medical Research Council Special Report Series No. 289. 70 pp. Illust. H. M. Stationery Office, London, 1955. 5/-.

JOURNAL OF

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The Editor reserves the right to make the usual editorial changes in manuscripts; these include such changes as are necessary to ensure correctness of grammar and spelling, clarification of obscurities or conformity to *Journal* style. In no case will major changes be made without prior consultation with the author. Authors will receive galley proofs of articles before publication, and are asked to confine alterations of such proofs to a minimum.

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References: Authors should limit references to published work to the minimum necessary for guidance to readers wishing to study the subject further. They should not quote articles they have never seen, and should set out references in a numbered list at the end of the article, thus:

1. Doakes, J.: *M. J. Kamchatka*, 1: 2, 1955, giving in order: (1) Author's name and initials in capitals. Where more than three authors are concerned in an article, only the first should be named, with *et al.* as reference to the others. (2) Cumulative Index Medicus abbreviation of journal name. (3) Volume number. (4) Page number. (5) Year.

References to books should be set out as follows:

Pickwick, S., *Textbook of Medicine*, Jones and Jones, London, 1st ed., p. 30, 1955.

Illustrations: Photographs should be glossy prints, unmounted and untrimmed, preferably not larger than 10 by 8 inches. Colour work can be published only at the author's expense. Magnification of photomicrographs must always be given. Photographs must not be written on or typed on. Identification can be made by pasting an identifying legend on the back. Patients must not be recognizable in illustrations, unless the written consent of the subject to publication has been obtained. Graphs and diagrams should be drawn in india ink on suitable white paper. Legends to all illustrations should be typed separately from the text of the article. Illustrations should not be rolled or folded.

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WANTED: STAFF ANÆSTHETIST.—Sunnybrook Hospital, D.V.A., for September 1956. For information in regard to salaries, etc., please communicate with the Superintendent, Sunnybrook Hospital, Toronto, Ontario.

RADIOLOGIST.—Assistant wanted for new metropolitan Toronto hospital. Must have three years' training or be certified. Good opportunity for young radiologist. Available immediately or by July 1, 1956. Give full details in letter to Box 764, Canadian Medical Association Journal, 150 St. George Street, Toronto 5, Ontario.

INTERNIST WANTED with certification or fellowship for an expanding group practice in Ontario. Experience in gastroenterology would be helpful. Apply stating experience, qualifications, starting salary expected, and include a recent snapshot if possible, to Box 763, Canadian Medical Association Journal, 150 St. George Street, Toronto 5, Ontario.

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ONTARIO CLINIC desires to add to its staff one internist and one general surgeon or urologist. Personal interview can be arranged for on June 12 or 13 at the Canadian Medical Association meeting in Quebec City by wiring to Box 758, Canadian Medical Association Journal, 150 St. George Street, Toronto 5, Ontario.

Continued on Page 36

CLASSIFIED ADVERTISEMENTS

WANTED: ASSOCIATE PATHOLOGIST.—Certified or eligible for St. Lawrence County, New York State. Salary $12,500-$15,000, depending on experience. United States Citizenship not required; eligibility for New York State License necessary. Write Dr. Robert T. Rogers, Director, St. Lawrence County Laboratories, Canton, New York, U.S.A.

WANTED.—Locum tenens for 2 years for busy general practice in Niagara Peninsula. Modern office; apartment; excellent hospital facilities. Owner leaving for postgraduate work. Reply giving age and experience to Box 681, Canadian Medical Association Journal, 150 St. George Street, Toronto 5, Ontario.

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APPLICATIONS ARE INVITED for an Assistant Professor in the Department of Anatomy. Experience in teaching and research in embryology and histology, or in neuroanatomy, is essential and a working knowledge of gross anatomy desirable. Candidates with a medical degree will be preferred, although those with an Honors Degree in medical science or biology will receive special consideration. The minimum salary for a medical graduate will be $5,000. The salary will depend on qualifications and experience. Applications to be made to Professor R. L. deC. Saunders, Anatomy Department, Dalhousie University, Halifax, Nova Scotia, Canada.

ASSOCIATE RADIOTHERAPIST required for expanding radiotherapy department in 600-bed general hospital in Eastern Canada. Applicants should give particulars of qualifications, experience, age, religion, marital status and recent testimonials should be included. State salary expected. Apply to Box 742, Canadian Medical Association Journal, 150 St. George Street, Toronto 5, Ontario.

APPLICATIONS ARE INVITED for the post of Medical Superintendent of the St. Lawrence Sanatorium, Cornwall, Ontario. Salary depending on qualifications and experience. Superannuation benefits provided. Candidates must have special knowledge of clinical and administrative aspects of tuberculosis and a license to practise in Ontario. Letters of application with relevant details of personal and professional history to be sent to the Secretary-Treasurer, Board of Governors, St. Lawrence Sanatorium, 20 Pitt Street, Cornwall, Ontario.

WANTED: A QUALIFIED PHYSICIAN AND SURGEON for a locum tenens July 9 to September 9, 1956. Salary $450 per month. Room and board supplied. Applicant please state age, qualifications and experience. Reply to Box 733, Canadian Medical Association Journal, 150 St. George Street, Toronto 5, Ontario.

WANTED.—Surgeon with certification or fellowship for expanding group in growing western city. Apply giving personal description, qualifications, experience, etc., to Box 732, Canadian Medical Association Journal, 150 St. George Street, Toronto 5, Ontario.

WANTED.—Medical assistant in group of three in Northwestern Ontario town. Permanent position to suitable applicant. Salary $500 per month with an increase at the end of the first year. One month's holidays with pay for each 12 months' service. Applicant should have his own car and will be paid for use of same on a negotiated mileage basis. All office expenses carried by the employer. Services to begin June 1, 1956. Address applications to Box 663, Canadian Medical Association Journal, 150 St. George Street, Toronto 5, Ontario.

WANTED.—Qualified specialist E. N. and T. for progressive, rapidly expanding, Southern Ontario clinic. Reply stating race, age, training and salary expected, to Box 684, Canadian Medical Association Journal, 150 St. George Street, Toronto 5, Ontario.

POSITION VACANT.—A vacancy exists on the active staff of this English speaking general hospital for a doctor with certification in E.N.T. or E.E.N.T. to take charge of the department. All tonsillectomies referred to the E.N.T. department. A new hospital, on a new site, of 150 beds, was occupied December 1955. For further details apply to: Administrator, Jeffery Hale's Hospital, 1250 St. Foy Road, Quebec 6, P.Q.

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WANTED: ANÆSTHETIST.—Well-established group in Central Ontario requires services of certified anæsthetist. Write stating remuneration requirements, experience and references to Box 562, Canadian Medical Association Journal, 150 St. George Street, Toronto 5, Ontario.

WANTED.—Urologist with certification or fellowship for a group in Ontario. Apply stating experience, qualifications, starting salary expected, and include a recent snapshot if possible. Box 540, Canadian Medical Association Journal, 150 St. George Street, Toronto 5, Ontario.

Positions Wanted

WANTED.—F.R.C.S. (Edinburgh), certified general surgeon R.C.S. (Canada); experienced in general and orthopædic surgery; desires association with group in British Columbia or Southern Ontario. Willing to share in general work in smaller group if necessary. Reply to Box 767, Canadian Medical Association Journal, 150 St. George Street, Toronto 5, Ontario.

WANTED.—M.B., B.Ch., B.A.O., L.M., D.R.C.O.G., eligible obstetrics and gynæcology certificate; very extensive hospital experience and six years with Royal Navy; wishes to join group, clinic or private practice at earliest opportunity. Age 36. Aim to build up large obstetrical and gynæcological practice, but willing and able to work any department meantime as a means to that end. Any suggestions will be very welcome. Reply to Box 766, Canadian Medical Association Journal, 150 St. George Street, Toronto 5, Ontario.

ENGLISH GENERAL PRACTITIONER specializing in obstetrics and gynæcology, with broad hospital experience, having decided to live in Canada, seeks post in small town. Ex-parachutist, age 30, Scots wife and two children. Apply to Dr. Martin-Smith, Manor House Hospital, London, N.W.11, England.

AVAILABLE FOR LOCUM TENENS or clinic work in Manitoba for two weeks to one month during July to September. Reply to Box 757, Canadian Medical Association Journal, 150 St. George Street, Toronto 5, Ontario.

POSITION WANTED.—F.R.C.S., trained in general surgery and urology. Available July 1956. Reply to Box 759, Canadian Medical Association Journal, 150 St. George Street, Toronto 5, Ontario.

LOCUM TENENS WANTED by University of Toronto graduate, L.M.C.C. (M.D.), completing one year junior rotating internship in June 1956. Available July 3-27, 1956 inclusive. Preferably in vicinity of Toronto East General Hospital. Reply to Box 760, Canadian Medical Association Journal, 150 St. George Street, Toronto 5, Ontario.

GERMAN, L.M.C.C., age 30, Protestant, single. Four years' internship and one year general practice. Qualified in surgery, but not certified. Wishes to do general practice and surgery anywhere in Canada. Available in late summer. Reply to Box 761, Canadian Medical Association Journal, 150 St. George Street, Toronto 5, Ontario.

CERTIFIED INTERNIST desires position with group in British Columbia. Reply to Box 762, Canadian Medical Association Journal, 150 St. George Street, Toronto 5, Ontario.

BRITISH MALE DOCTOR, M.Ch., F.R.C.S. (England), M.R.C.P.; married, age 35; 10 years' hospital experience including 8 years' surgical, general and thoracic; seeks opening in surgery with future in Canada. Ontario preferred. Energetic, capable of and used to hard work. Available soon. Reply to Box 706, Canadian Medical Association Journal, 150 St. George Street, Toronto 5, Ontario.

EXPERIENCED GENERAL PRACTITIONER, Canadian graduate 1943, desires to purchase active practice in city or large town. Single or two man practice, or partnership considered. Reply to Box 749, Canadian Medical Association Journal, 150 St. George Street, Toronto 5, Ontario.

GENERAL PRACTITIONER, age 30, L.M.C.C., with 2 years' successful Canadian practice, seeks first class association or purchase practice in medium size town. Experience in surgery, writing and finance. Available second half July. Reply to Box 741, Canadian Medical Association Journal, 150 St. George Street, Toronto 5, Ontario.

POSITION WANTED.—Assistantship in general practice, group practice or locum tenens anywhere in Canada. Canadian, recent graduate with one year postgraduate medicine. Reply to Box 754, Canadian Medical Association Journal, 150 St. George Street, Toronto 5, Ontario.

(Continued on page 38)

CLASSIFIED ADVERTISEMENTS

LOCUM TENENS WANTED by McGill graduate, age 30. Available all or part of months July to December, anywhere in Canada where license can be arranged. L.M.C.C. and Quebec license; speaks fair French; has own car. Reply to Dr. Peter Burgess, Montreal Children's Hospital, Montreal, Quebec.

POSITION WANTED.—Recent Alberta graduate, two years' rotating internship with training in anæsthesia, desires position with established general practitioner or small group. Married. Available July 1, 1956. Alberta, British Columbia or Saskatchewan preferred. Write to Box 753, Canadian Medical Association Journal, 150 St. George Street, Toronto 5, Ontario.

PRECEPTORSHIP WANTED.—Graduate Toronto 1955, conscientious, hard worker, completing internship in a large American county hospital, wishes an assistantship with a surgeon or group of surgeons starting July 1956. Reply to Box 688, Canadian Medical Association Journal, 150 St. George Street, Toronto 5, Ontario.

Practices

EXCELLENT OPPORTUNITY FOR DOCTOR.—(Physician, surgeon, general practitioner or specialist) desirous of settling in Niagara Peninsula. Progressive community, growing rapidly. Two good hospitals. Property comprises solid brick house and large garage, part of which is now rented for $35 per month. Upper floor of house is a self-contained, five-room apartment, now held vacant pending sale. Lower floor suitable for offices—one or two suites. Situation is up town, in good professional neighbourhood. Price $35,000. If interested, write, phone or wire, Lloyd H. Werden, M.D., 189 King Street, St. Catharines, Ontario.

FOR SALE.—General practice in Niagara Peninsula. Should gross $35,000. No capital required; no real estate to buy. Owner specializing. Reply to Box 679, Canadian Medical Association Journal, 150 St. George Street, Toronto 5, Ontario.

FOR SALE.—Active general practice on rental basis. Capable of supporting two doctors. Southern Ontario. Owner leaving to specialize. Reply to Box 680, Canadian Medical Association Journal, 150 St. George Street, Toronto 5, Ontario.

GENERAL PRACTICE FOR SALE.—Excellent opportunity for young doctor who wishes to establish in the city of Winnipeg. Very reasonable arrangements. Available June 1, or July 1, 1956. Reply to Box 724, Canadian Medical Association Journal, 150 St George Street, Toronto 5, Ontario.

FOR SALE.—Southern Saskatchewan city. Partnership in well-established general practice (of 2 members). New, modern, 80-bed union hospital. New, modern, 7-room house including, 3 large bedrooms and den upstairs. Leaving to specialize. Reply to Box 714, Canadian Medical Association Journal, 150 St. George Street, Toronto 5, Ontario.

PRACTICE VACANT in July in prosperous agricultural area, 70 miles from Toronto. Large potential. No capital required. House and office combined, available for rent. Owner leaving to specialize. Reply to Box 746, Canadian Medical Association Journal, 150 St. George Street, Toronto 5, Ontario.

FOR SALE IMMEDIATELY.—Established and growing remunerative E.N.T. practice in large western capital. Wonderful opportunity in ever expanding town. Office and equipment available. Good hospital facilities. Reply to Box 740, Canadian Medical Association Journal, 150 St. George Street, Toronto 5, Ontario.

FOR SALE.—Well-established general practice grossing $25,000 yearly. County seat town of 2,000 serving large area. Modern 35-bed hospital. Well-equipped office; rented quarters. No waiting to build up practice. Available immediately. Write Mrs. A. D. Strom, Langdon, North Dakota, U.S.A.

FOR SALE OR RENT.—Well equipped office for general practice in prosperous central Alberta. Appointments in accredited open hospitals available. Owner specializing. Please reply to Box 736, Canadian Medical Association Journal, 150 St. George Street, Toronto 5, Ontario.

FOR SALE.—General practice in modern office building in Toronto. Very reasonable, at value of equipment. Ideal for European doctor who speaks German. Reply to Box 744, Canadian Medical Association Journal, 150 St. George Street, Toronto 5, Ontario.

FOR SALE.—Small, fully equipped medical clinic. Eastern section of Toronto. Established 25 years. X-ray equipment and operating room for minor surgery. Gross income about $30,000. One assistant on percentage basis. Owner retiring. Reply to Box 677, Canadian Medical Association Journal, 150 St. George Street, Toronto 5, Ontario.

CLASSIFIED ADVERTISEMENTS

Internships and Residencies

APPROVED JUNIOR ROTATING INTERNSHIP available July 1956, in medicine, surgery, pædiatrics, obstetrics and pathology. 181 beds and bassinettes. Apply Administrator, St. Michael's General Hospital, Lethbridge, Alberta.

WANTED SENIOR INTERN OR ASSISTANT RESIDENT in anæsthesia for July 1, 1956 to June 30, 1957. Salary for the senior intern is $1,800 per annum; assistant resident is $2,700. Please address communications to Superintendent, Sunnybrook Hospital, Toronto, Ontario.

THE ROYAL JUBILEE HOSPITAL offers approved junior rotating internships, with an organized training program. Stipend $100 per month with full maintenance and $25 a month living out allowance for married interns. For further information apply to the Medical Administrator, Royal Jubilee Hospital, Victoria, British Columbia.

ANÆSTHESIOLOGY RESIDENCIES at the University of Minnesota Medical Center. Two or three year program with clinical and didactic instruction in all phases of anæsthesia. Board approval. Positions starting every month. Address: F. H. Van Bergen, M.D., University of Minnesota Medical Center, Minneapolis 14, Minnesota, U.S.A.

POSITION AVAILABLE as resident in a 250-bed hospital for a Canadian graduate who has completed one year of rotating internship. Remuneration $300 per month plus maintenance. For further details contact Superintendent, Oshawa General Hospital, Oshawa, Ontario.

RESIDENCIES IN ANÆSTHESIA. — The Department of Anæsthesia of the Royal Victoria Hospital, Montreal, offers approved residencies of one or two years' duration. Previous rotation service is required and preference is given to those who have had experience in practice. Appointments available to commence July 1, 1956, and January 1, 1957. Salary and maintenance. For information apply to the Executive Director, Royal Victoria Hospital, Montreal 2, Quebec.

RADIOLOGY RESIDENCY available at Michael Reese Hospital, Chicago 16, Illinois. Fully approved teaching program including rotation through Department of Radiotherapy. 900-bed general hospital plus large outpatient service. Apply: Medical Director.

ONE ANÆSTHESIA RESIDENCY AND ONE EYE RESIDENCY, unexpectedly available for July 1956, in 900-bed hospital with active teaching and research programs. If interested write Medical Director, Michael Reese Hospital, Chicago 16, Illinois, U.S.A.

VACANCY FOR ASSISTANT RESIDENT IN: (1) service of pædiatrics. (2) service of obstetrics. Modern 800-bed general hospital. Excellent opportunity for experience. Training approved by the Royal College of Physicians and Surgeons of Canada. Salary: $150 per month, plus full maintenance. Applications to: Director of Medical Education, or, Superintendent, Regina General Hospital, Regina, Saskatchewan.

VACANCY FOR RESIDENT IN: (1) service of pædiatrics. (2) service of obstetrics. Modern 800-bed general hospital. Excellent opportunity for experience. Training approved by the Royal College of Physicians and Surgeons of Canada. Salary: $200 per month, plus full maintenance. Applications to: Director of Medical Education, or, Superintendent, Regina General Hospital, Regina, Saskatchewan.

RESIDENCIES VACANT IN PSYCHIATRY.—Active treatment department of 600-bed general hospital. Organized training approved by Royal College. $1,800 per annum and full maintenance. Apply to Sister Superior, Ottawa General Hospital, Ottawa, Ontario.

ST. LUKE HOSPITAL in Montreal, capacity of 451 beds, is considering applications for internship or residencies in the different services of a general hospital and most specially in the following services where the teaching is approved by the American College of Surgeons: surgery, medicine, obstetrics, oto-rhino-laryngo-ophthalmology, pathology and radiology. Applicants may address their applications to Doctor H. I. Tétreault, Medical Superintendent.

INTERNSHIPS IN A GENERAL HOSPITAL.—Youville Hospital, Noranda, Quebec, 225 beds, operated by Grey Nuns of the Cross, requires a senior and junior intern, bilingual. Salaries $400 and $300 per month plus maintenance. Hospital provisionally accredited. Apply to Secretary, Medical Society, Youville Hospital, Noranda, Quebec.

MEDICAL NEWS *in brief*

(Continued from page 926)

BIOFLAVONOIDS IN OTOLARYNGOLOGY

Goldman of New York (*Eye, Ear, Nose and Throat Monthly*, 35: 246, 1956) reports the administration of a bioflavonoid compound (C.V.P.) at 530 tonsillectomies. The compound was given by mouth as a syrup containing 100 mg. ascorbic acid, 100 mg. bioflavonoid and 0.66 mg. menadione per teaspoonful, for children, or as a capsule containing the ascorbic acid and bioflavonoid with a separate capsule containing 5 mg. menadione. Children received one teaspoonful of the syrup three times a day for six to eight days before operation and for four days afterwards. Adults were given two capsules four times a day. The author is under the impression that there was a decided decrease in oozing after the tonsil surfaces had been cut and that the use of a clamp and tie was less common than in controls. He also used this compound in 35 cases of nasal operation for nasal polyps, septal straightening etc. and again found that the use of sutures on nasal packing became less common and that postoperative swelling appeared to disperse more rapidly. The compound is also suggested for recurrent epistaxis.

DIETARY FAT AND CARDIOVASCULAR DISEASE

The role of a high fat diet in the production of cardiovascular disease is still badly understood, but there is a substantial body of opinion which suggests that a high fat diet is detrimental to the well-being of the middle-aged. The Department of Nutrition, Pretoria, South Africa, has issued a statement in which it points out that the calories derived from fat, expressed as a percentage of the total calories in the diet, vary between 8% in Japan and 40% in the United States. Heart and arterial diseases are very rare with the Japanese and very prevalent in the United States. The Department of Nutrition, therefore, issues a general warning to the public as to the level of fat desirable in the diet. We quote from this warning as follows:

"Expert opinion places the safety level of fat intake for adults at 20-30% of the total calories. In the case of very active persons or children it may safely be increased to 40%. In terms of food this means that fatty foods should be taken in moderation, especially by adults with a sedentary occupation and those who are moderately active; eat bread and butter and not butter with bread; one rich sauce or one fried dish in a meal is sufficient for the middle-aged, inactive person and perhaps more than enough; be satisfied with very little fat on the meat; bacon lends a pleasant flavour to a dish and, if served wisely, it will be enjoyed for many more years; tea parties are meant for social intercourse and not to shorten lives, for the fat content of cakes, pastries and savouries is very high; whipped cream increases in volume and therefore a smaller quantity will satisfy than when it is served unwhipped over dessert.

"It would be unwise to exclude nutritious food such as milk, cheese and eggs from the diet for fear of a too high fat content, when methods of preparation and snacks at parties are the real culprits.

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MEDICAL NEWS *in brief*

(Continued from page 43)

"Hardening of the arteries and coronary thrombosis as one of the serious consequences, is a threat to Western civilization. An excessive intake of fat appears to be one of the most important causative factors in the deterioration of the blood vessels. It would, therefore, be wise to become accustomed to a dietary pattern which affords a less important place to fat than is the case at present."—*South African M. J.*, 30: 276, 1956.

AMERICAN COLLEGE OF PHYSICIANS

At the 37th Annual Session of the American College of Physicians in Los Angeles, California, April 16-20, 1956, there was a gross attendance of over 4,500. Dr. Walter L. Palmer of Chicago was inducted as President with Dr. Chester M. Jones of Boston as President-elect. The 1957 Annual Session will be held at Boston, Mass., on April 8-12. The following is the list of Canadian physicians who were elected to Fellowship or Associate Membership at the annual meeting: Joachim O. W. Brabander, Montreal, Que.; Ronald V. Christie, Montreal, Que.; William Carleton Gibson, Vancouver, B.C.; Ronald Hugh McFarlane, Winnipeg, Man.; John Christian Beck, Montreal, Que.; Alex Belkin, Calgary, Alta.; Kenneth William Gordon Brown, Toronto, Ont.; Lauder Brunton, Montreal, Que.; Leslie Jerome Cera, Winnipeg, Man.; Paul Owen Crossfield, Calgary, Alta.; Charles Alexander Gordon, Halifax, N.S.; Louis Horlick, Saskatoon, Sask.; Paul Harvey Kepay, Vancouver, B.C.; Wilfred Leith, Montreal, Que.; Edward Daniel Ring, Regina, Sask.; Douglas Leonard Roy, Halifax, N.S.

CANADIAN CANCER RESEARCH CONFERENCE

The Second Canadian Cancer Research Conference will be held at Honey Harbour, Ontario, June 17-21, 1956. Sponsored by the National Cancer Institute of Canada, this conference is primarily designed to encourage a review of present knowledge on various aspects of cancer for the benefit of grantees of the Institute. The topics to be discussed include the cell, leukæmia and chemotherapy, hormones and cancer, and immunity and basic mechanisms. Since accommodation is limited, attendance must be by application only. Further information may be obtained from Dr. Robert L. Noble, Collip Medical Research Laboratory, University of Western Ontario, London, Ontario, Canada.

AWARD IN HOSPITAL ADMINISTRATION

President Sidney E. Smith of the University of Toronto has announced the setting up of an annual award of $1,000 for the outstanding student in the University's Graduate Course in Hospital Administration. This award is to be known as the Robert Wood Johnson Award and has been made available through the generosity of the officers and board of Johnson & Johnson Limited, well-known manufacturers of surgical dressings and supplies.

The award will be given at the end of the second or residency year and will be conferred upon that member of the class who gives the most promise of making a real contribution towards the advancement of hospitals and hospital administration. Consideration is to be given to personal attributes and academic standing. This award will be made by the Director of the School of Hygiene upon the recommendation of the Department of Hospital Administration.

CONFERENCE ON AGING

The University of Michigan announces its Ninth Annual Conference on Aging to be held in Ann Arbor, Michigan, July 9-11, 1956. It will have as its topic "Health for the Aging—Medical and Social Services". Several units of the University of Michigan, the Michigan State Medical Society and a number of state and federal agencies are co-sponsoring this meeting, together with the Division of Gerontology of the University of Michigan. The program will consist of general sessions on health topics, clinics on medical topics of concern to physicians, psychiatrists,

dentists, nurses, occupational therapists, and other specialists, and workshops in the areas of health services, welfare programs, institutional care, community health planning, geriatric training of medical and other personnel. There will also be a research seminar with participation by outstanding scientists on the health status and needs of the aging population. For further information apply to Dr. Wilma Donahue, Division of Gerontology, 1510 Rackham Building, Ann Arbor, Michigan, U.S.A.

AUTOMOBILE SEAT BELTS

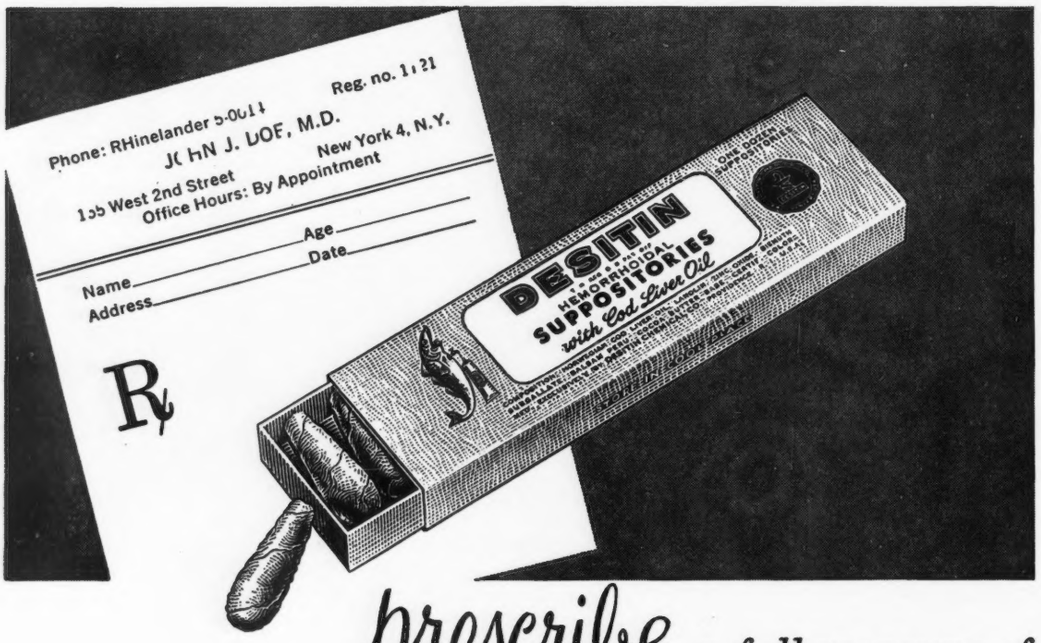
It has been shown by police investigators that about two-thirds of the victims in fatal automobile crashes might have survived if they had been wearing good seat belts. There has recently been a great swing from complete rejection of seat belts to widespread acceptance, and belts are now offered by many automobile manufacturers as an optional extra. These belts have been endorsed by the U.S. National Safety Council, the American Medical Association, the American College of Surgeons, major insurance companies and other groups. It is therefore necessary to go into the question somewhat more deeply and to study the design of seat belts of various manufacturers.

Consumer Reports in its May 1956 issue discusses the testing of 39 varieties of seat belt offered on sale in the United States; some are offered as an extra by well-known manufacturers. It is sad to record that in testing, 26 out of the 39 belts failed to meet with the approval of *Consumer Reports* testers. The usual trouble was that the buckle slipped or broke or webbing broke. Among seat belts found unacceptable were a number offered as optional equipment by automobile manufacturers. Anyone contemplating installation of seat belts or wishing to recommend them to others should study this informative article before deciding.

FREUD AND MODERN THOUGHT

May 1956 marked the centenary of the birth of Sigmund Freud. We note with interest that the

(Continued on page 50)



prescribe *a full measure of comfort for anorectal patients with*

DESITIN®

hemorrhoidal SUPPOSITORIES with cod liver oil

In boxes of 12 foil-wrapped suppositories

samples yours for the asking

DESITIN SUPPOSITORIES quickly soothe, protect, lubricate the distressed anorectal mucosa to provide.....

- **gratifying comfort in hemorrhoids** (non-surgical)
- **rapid, sustained relief of pain, itching and spasm without styptics, local anesthetics or narcotics, therefore do not mask serious rectal disease**
- **reduced engorgement, bleeding • safe, conservative**

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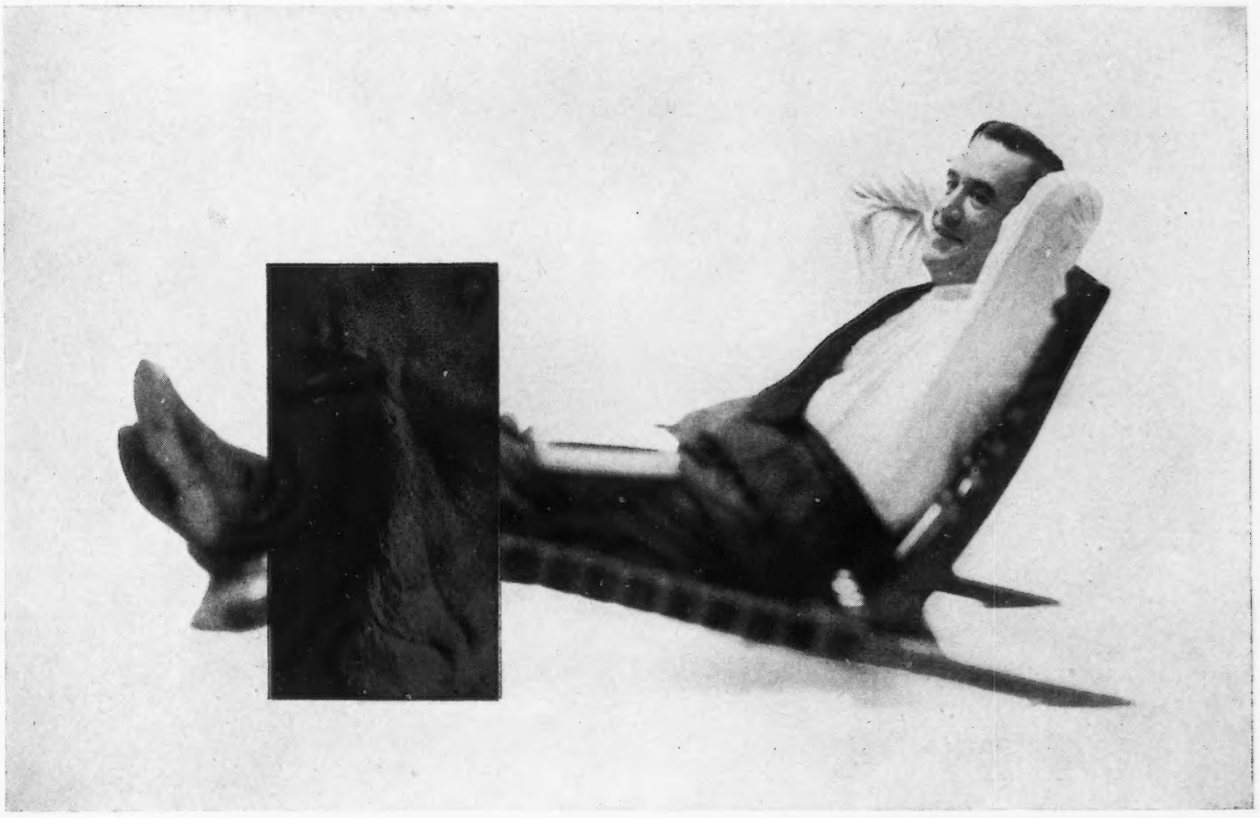
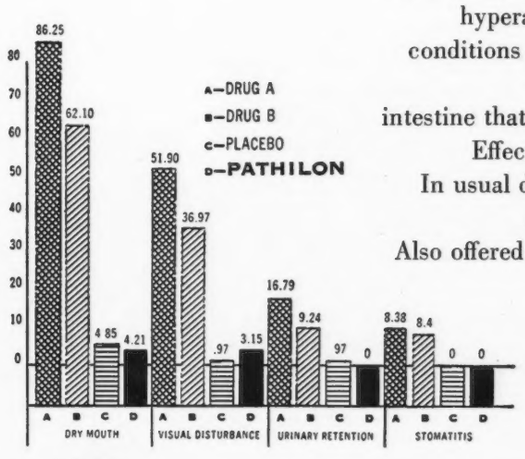


ulcer relief with few side effects[1] *!*

new **PATHILON***

Iodide
Tridihexethyl iodide *Lederle*
Tablets 25 mg.



For the medical management of peptic ulcer, gastric hyperacidity and hypermotility, gastrointestinal spastic conditions such as spastic and irritable colon, functional diarrhea, pylorospasm, and hypermotility of the small intestine that is not associated with organic change.[2]

Effective in relieving pain due to smooth muscle spasm. In usual dosage, undesirable side effects are rare.

Available with or without added phenobarbital, 15 mg.

Also offered as PATHILON Parenteral, 10 mg./cc.—1 cc. ampuls.

1."Evaluation of Drugs in the Treatment of Peptic Ulcer" by J. M. Ruffin, M. D.; D. Cayer, M. D.; J. S. Atwater, M. D., and B. G. Oren, M. D., Exhibit at A.M.A. Meeting, Atlantic City, June, 1955.
2. J.A.M.A. 160:389 (Feb. 4) 1956

Lederle LEDERLE LABORATORIES DIVISION, *NORTH AMERICAN Cyanamid LIMITED*, MONTREAL, QUEBEC

*REG. TRADE-MARK IN CANADA

Canad. M. A. J.
June 1, 1956, vol. 74

MEDICAL NEWS *in brief*

(Continued from page 45)

series "Architects of Modern Thought", broadcast last year by the Canadian Broadcasting Corporation in its Wednesday night program, is now available in print (CBC Publications Branch, Toronto; 50 cents per copy) and includes lectures on Freud, Darwin, Marx, William James, Einstein, Dewey, Maritain, Sartre, Tillich, Spengler, and Bertrand Russell. The talk on Freud is given by Dr. Clifford Scott of Montreal. Dr. Scott discusses briefly the life and work of Freud with its implications for the modern world. Many years after the beginning of Freud's work psychoanalysis still faces opposition and the number of trained psychoanalysists is still quite small in Canada (in the U.S.A. there are only 500 qualified psychoanalysts). The psychoanalysis of children has begun and is increasing in volume, and psychoanalysts of different religious backgrounds are beginning to share their experiences. He points out that psychoanalysts are well aware of the economic problems in psychotherapy and are actively working to solve the problem of how to increase the speed of human change—the speed of mourning, the speed of changing beliefs, and the speed of overcoming a fear or an obsession. As long as so much money goes for research in destruction, says Dr. Scott, psychoanalysts can hope that eventually more will go into the vast field of opportunities sown by Freud.

—

MENTAL HEALTH IN NEW YORK

Workers in the field of mental health will note with the greatest of interest the fact that during the last year the records of the New York State Department of Mental Hygiene show a decrease in the number of mental hospital patients. This may prove to be merely a temporary fluctuation, but there is hope that it may represent a reversal in the current trend, whereby the number of admissions to mental hospitals has each year considerably surpassed the number of discharges from such institutions. In the year March 31, 1955 to March 31, 1956 there was an increase of 2,600, or 23%, over the previous year in the number of patients discharged from hospital. The improvement in discharge rates is attributed to intensified treatment, including more extensive use of the new tranquillizing drugs.

—

COURSE IN OCCUPATIONAL MEDICINE

A full-time eight-week comprehensive course in occupational medicine for physicians will be given at the Post-Graduate Medical School of New York University-Bellevue Medical Center, September 10-November 2, 1956. Subjects discussed will include organization and administration of an industrial medical department, preventive medicine in industry, occupational diseases, industrial toxicology and hygiene, statistics and epidemiology. Opportunity will be provided for attendance at medical, surgical and clinico-pathological conferences during the course. Information from: the Dean, N.Y.U. Post-Graduate Medical School, New York 16, N.Y. The course costs $350.

—

POST-EMOTIONAL PEPTIC ULCER AND ULCERATIVE COLITIS

Moutier and his colleagues (*Presse méd.*, 64: 585, 1956) report eight cases in which the onset of peptic ulcer or of ulcerative colitis followed within days of severe emotional shock (sudden death of a near relative, broken engagement, serious accident). In eight cases the stomach or duodenum was affected and in two the colon; they find it impossible to say why these organs were selected rather than others. In no case was there any history of neurosis previously. They find it impossible to subscribe to the statement of Tidy that psychoneurotic stimuli may pull the trigger, but something else has loaded the rifle. They envisage a violent arterial constriction in the region of the viscus affected, and point out that in the case of retinal artery spasm, quite a brief spasm may produce irreversible lesions.

—

SCHERING AWARD WINNERS

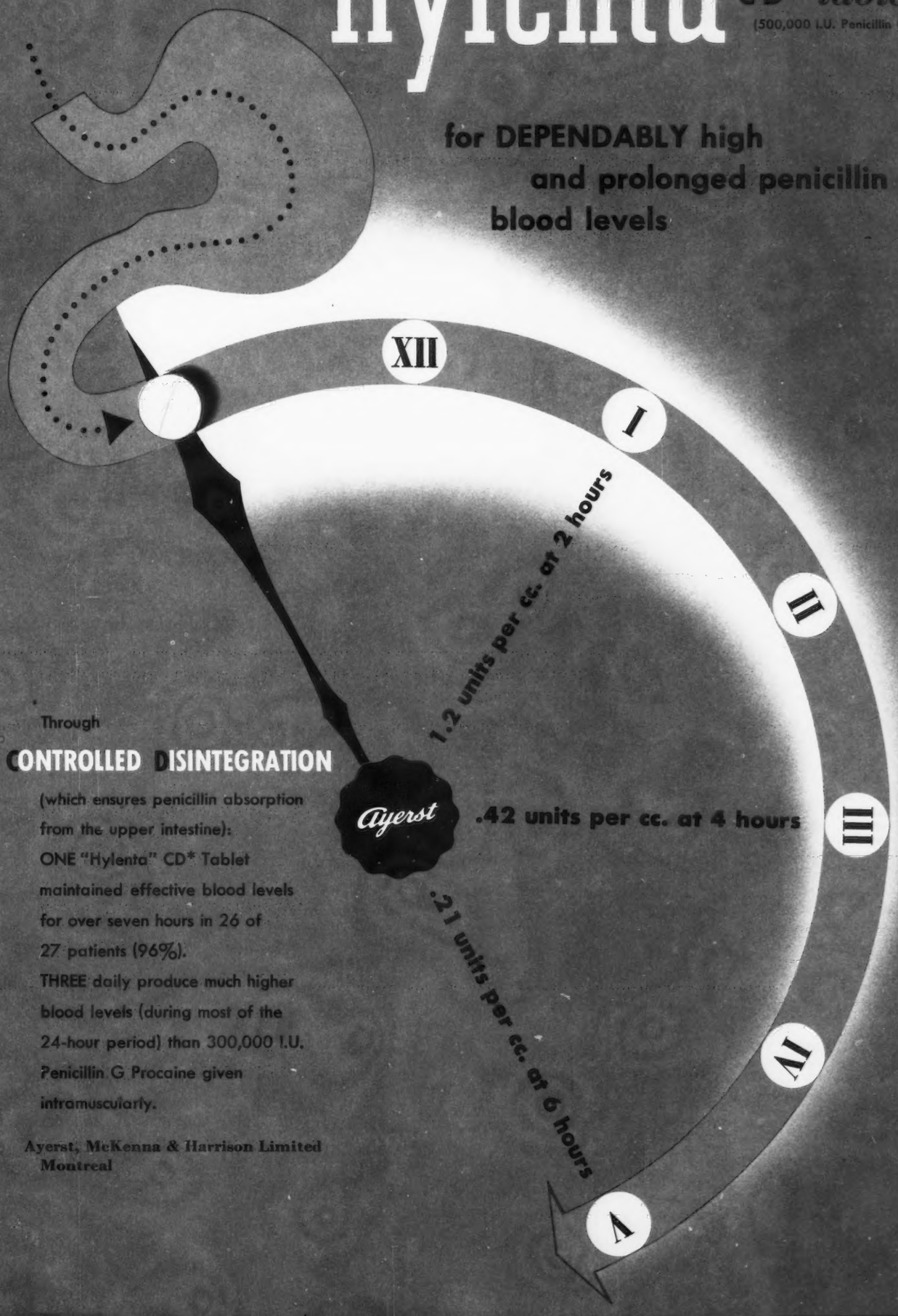
Two medical students who submitted joint papers have been an-

(Continued on page 53)

"Hylenta" CD* tablets

(500,000 I.U. Penicillin G Potassium)

for DEPENDABLY high and prolonged penicillin blood levels



* Through **CONTROLLED DISINTEGRATION** (which ensures penicillin absorption from the upper intestine):

ONE "Hylenta" CD* Tablet maintained effective blood levels for over seven hours in 26 of 27 patients (96%).

THREE daily produce much higher blood levels (during most of the 24-hour period) than 300,000 I.U. Penicillin G Procaine given intramuscularly.

Ayerst, McKenna & Harrison Limited
Montreal

cut the convalescent period

Patients who receive vitamin B complex and C have a much smoother and more comfortable postoperative course. In one series*, such patients recovered more promptly from anesthesia and experienced a return of appetite on an average of 1.9 postoperative days as compared with 4.0 days for the control group.

Ayerst, McKenna & Harrison Limited, Montreal

"Beminal" WITH C FORTIS

No. 817

"eight-seventeen"

Ayerst

*J. National Med. Assoc. 42:140 (May) 1950.

MEDICAL NEWS *in brief*

(Continued from page 50)

nounced as winners of the 1955 Schering Award, open to all medical students in the United States and Canada. Now in its 11th year, the contest annually awards three $500 first prizes and $250 second prizes for the best papers submitted on three selected medical topics of current interest.

Successful contestants, Charles King Mervine and David Charles Schechter, both attending Jefferson Medical College in Philadelphia, co-authored the two prize-winning papers, topping entries from more than 80 other medical schools. Subjects of their papers were "The Prevention and Treatment of Blood Transfusion Reactions" and "The Management of Osteoporosis".

"It is most extraordinary that for the first time in the history of the Award, two students from the same school have taken first prizes for reports in two of the three given medical subjects," declared Chester J. Szmal, M.D., chairman of the Award committee.

The paper taking third prize was written jointly by Frank A. Migliorelli of Georgetown Medical School, Washington, D.C., and Salvatore Leone of the State University of New York College of Medicine at Brooklyn.

The 11th annual Schering Award competition is now under way. Subjects this year are: "The Clinical Use of Adrenocortical Steroids in Collagen Diseases"; "Metabolic Aspects of the Aging Process"; and "New Applications of Antihistamines in Medicine and Surgery". The Award's aim is to encourage medical writing in the hope that later during their careers many of the students will contribute to the professional literature.

AMERICAN BOARD OF OBSTETRICS AND GYNÆCOLOGY

Applications for certification (American Board of Obstetrics and Gynæcology) for the 1957 Part I Examinations are now being accepted. All candidates are urged to make such application at the earliest possible date. Deadline date for receipt of applications is October 1, 1956.

Candidates for admission to the Examinations are required to submit with their application, a plain typewritten list of all patients admitted to the hospitals where they practice, for the year preceding their application or the year prior to their request for the re-opening of their application.

Application for re-examination, as well as requests for resubmission of case abstracts, must be made to the Secretary before October 1, 1956.

Current Bulletins outlining present requirements may be obtained by writing to the Secretary's office: Dr. Robert L. Faulkner, Secretary, American Board of Obstetrics and Gynæcology, 2105 Adelbert Road, Cleveland 6, Ohio.

THE DAY HOSPITAL

At the end of 10 years' operation, the Day Hospital, which was

(Continued on page 54)

MEDICAL NEWS *in brief*

(Continued from page 53)

first established in the Allan Memorial Institute (Royal Victoria Hospital) has been reviewed. It has been exceedingly successful, and similar Day Hospitals have now been established in Canada, the United States and Britain. Patients come from 9 to 5 each day except Sunday. All types of patients that can be admitted to a day and night division of a general hospital can be accepted in a day hospital, and all forms of treatment with the possible exception of coma insulin, can be carried on in the day hospital. The cost to the patient is about one-half to one-third of that to the patient who has to reside overnight.

ASSSEMBLY IN OTOLARYNGOLOGY

The Department of Otolaryngology, University of Illinois College of Medicine, announces its Annual Assembly in Otolaryngology, October 1-7, 1956. The Assembly will consist of an intensive series of lectures and panels concerning advancements in otolaryngology, and evening sessions devoted to surgical anatomy of the head and neck, and histopathology of the ear, nose and throat.

Interested physicians should write direct to the Department of Otolaryngology, 1853 West Polk Street, Chicago 12, Illinois.

TITANIUM SALTS IN DERMATOLOGY

Drs. Poirier and Baillargeon of Montreal *(Union Médicale Canada,* 85: 443, 1956) present a preliminary report of their experience with a titanium oinment and cream (Metanium) and report favourably on their experience in 90 cases. Their series included six cases of acute dermatitis venenata which responded satisfactorily, eight cases of intertrigo, some of which responded well, 20 cases of diaper rash with rapid improvement in 18, 15 cases of eczematoid dermatitis with excellent results in all but three cases, and some cases of seborrhœic dermatitis and atopic dermatitis. In four cases of epidermolysis bullosa, the ointment brought about improvement where previous topical applications had failed. The product did not lead to irritation or sensitization.

A WORTHY CAUSE

(We reproduce the following appeal with the permission of "Canadian Hospital"—Ed.)

Here in Canada there is an unlimited supply of medical and surgical equipment of every type. No patient need suffer from the lack of the wherewithal to provide adequate treatment.

In many foreign countries, however, this is not the case. It was this need that brought into being the Evangelical Medical Missionaries' Aid Society with headquarters at 989 Bay Street, Toronto, whose object it is to supply free of charge good, used (and in some instances new) equipment to physicians, surgeons, and dentists in the Mission Field. These men frequently find their work handicapped by this lack. As an example of the work being done, this organization has recently served as the clearing house for the Canadian Red Cross Society which donated several thousand blood-transfusion sets of a type still very useful but recently replaced in this country by a more modern disposable type. These sets now on their way to such countries as India, Africa, Ecuador, and elsewhere may well prove lifesavers in many instances and at the same time bring joy to the hearts of those surgeons who use them.

May we suggest, therefore, that our readers go through their instrument drawers to see if there may be lying about unused, but still usable, instruments and other equipment which may be channeled through this organization to serve a more useful purpose than simply occupying space here at home.

In addition to such used equipment interested surgical supply houses have offered the organization from time to time at bargain prices good, new instruments of a type recently replaced in this country by something more modern. In order to take advantage of these offers donations of cash are most acceptable. Such donations are tax exempt and should be sent to the secretary-treasurer, Dr. R. A. Clappison, 307 Medical Arts Building, 170 St. George Street, Toronto. Instruments, on the other hand, should be sent to the organization at 989 Bay Street, Toronto.

A Lion, Ass and Fox

A Lion, an Ass and a Fox ran down a Stag and the Ass was to divide the Prey. As he was doing this Honestly and Innocently, into three equal Parts, the Lion fell on and kill'd him. Then the Lion bad the Fox divide: who had the wit to put the Whole to the Lion's Share, saving only a Miserable Pittance for him self.

The Moral: "*The Folly of one Man makes another Man wise*"

Doubly wise then is he who profits by the wisdom of others in recognizing established quality.

For Low Fat Diets

Borden's Starlac is an easily digested, highly palatable skim milk powder of prescription quality. Starlac is the most economical source of protein available, and is superior to ordinary skim milk in

- **Flavour**
- **Texture**
- **Solubility**

STARLAC—APPROXIMATE COMPOSITION

	Dry	Reconstituted*
Protein	36.5%	3.5%
Lactose	52.0%	5.0%
Milk Fat	1.0%	0.1%
Minerals	8.0%	0.8%
Calcium	1.3%	0.13%
Phosphorus	1.0%	0.1%
Moisture	2.5%	90.6%
Calories (per oz.)	103	11

*(4 oz. by weight to 40 oz. water—1 qt.)

Other Borden's Formula Foods

Dryco•Lactic Acid Milk Powder (C.M.P. Brand)**•Evaporated Milk**
Nutrilac • Mull-Soy • Protein Milk Powder (C.M.P. Brand)

For detailed information on
Borden's Formula Foods, write

THE BORDEN COMPANY, LIMITED

Formula Foods Dep't., Spadina Crescent,
Toronto, Ontario

When clinical judgment suggests Penicillin

"MEGACILLIN"
BRAND

a stable suspension of
Benzathine Penicillin-G

ONE MILLION UNITS
per teaspoonful

In recommended dosage by oral administration, Megacillin provides sufficiently large amounts to achieve high penicillin blood levels and therapeutic response with convenience, comfort and relative safety.

FOR CHILDREN AND ADULTS... "MEGACILLIN" SUSPENSION

Each 5 cc. teaspoonful contains:

Benzathine penicillin-G..... 1,000,000 I.U.

DOSAGE: One-half to one teaspoonful 3 to 4 times daily as the severity of the infection indicates.

Bottles of 60 cc.

FOR INFANTS... "MEGACILLIN" DROPS

Each 20 drops (1 cc.) contain:

Benzathine penicillin-G..... 200,000 I.U.

DOSAGE: Twenty drops for each 4 pounds of body weight per day in divided doses e.g., child weighing 16 lb. — 20 drops every 6 hours.

Bottles of 10 cc. with precision dropper.

CAUTION

In rare instances the injection of penicillin, and more rarely still its oral administration, may cause acute anaphylaxis. The reaction appears to occur more frequently in patients with bronchial asthma and other allergies, or in those who have previously demonstrated sensitivity to penicillin.

Frosst

Charles E. Frosst & Co.
MONTREAL CANADA

MOST EFFECTIVE
SAFER
ECONOMICAL

FOR THE TREATMENT OF
INFECTION

"TRULFACILLIN" BRAND

TRIPLE SULFAS and PENICILLIN

in the treatment of **PNEUMOCOCCIC, STAPHYLOCOCCIC, GONOCOCCIC and HEMOLYTIC STREPTOCOCCIC INFECTIONS**

•

SCARLET FEVER, OTITIS MEDIA, TONSILLITIS, VINCENT'S ANGINA and URINARY TRACT INFECTIONS

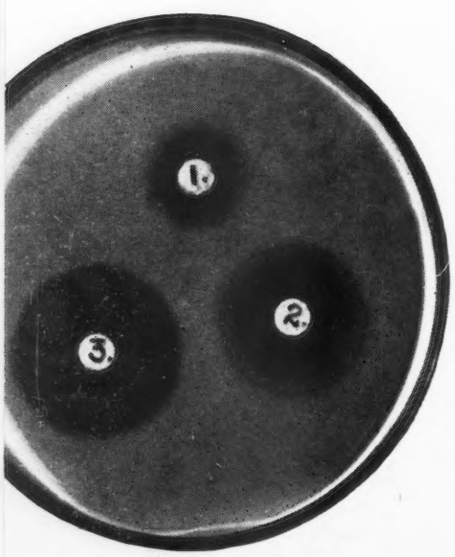
•

and for the prevention of **SECONDARY INFECTIONS during INFLUENZA, MEASLES and WHOOPING COUGH**

MOST EFFECTIVE — BROAD SPECTRUM OF ACTIVITY achieved by a two-pronged attack on infecting organisms ". . . . duration of treatment was considerably shortened with combined chemo and antibiotic therapy."*

SAFER—VIRTUAL FREEDOM FROM REACTIONS as compared with such broad spectrum antibiotics as oxytetracycline, chlortetracycline and tetracycline.

Fungal overgrowth, especially by monilia, — a very real danger — does not occur.



Culture plate showing inhibition of growth of Staph. aureus No. 209 by: (1) 1.0 mg. triple sulfonamides (2) 0.5 unit penicillin-G (3) 1.0 mg. triple sulfonamides *plus* 0.5 mg. penicillin-G.

* Lingard, W.F., The Treatment of Urinary Tract Infections, Canad. M.A.J., 74:353, 1956.

◀ ***WHEN PENICILLIN ALONE IS INDICATED***

Charles E. Frosst & Co.
MONTREAL CANADA

"TRULFACILLIN"

TABLETS

Each tablet contains:

Sulfamethazine ..... 167 mg.
Sulfadiazine ..... 167 mg.
Sulfamerazine ..... 167 mg.
} **7½ gr.**

Crystalline potassium penicillin-G
- **100**,000 I.U. — "TRULFACILLIN" 7½-100
- **150**,000 I.U. — "TRULFACILLIN" 7½-150
- **200**,000 I.U. — "TRULFACILLIN" 7½-200
- **300**,000 I.U. — "TRULFACILLIN" 7½-300

DOSE: One or two tablets every 4 to 6 hours. Trulfacillin tablets should be administered one-half hour before or two hours after meals.

Boxes of 12 tablets. Each tablet is sealed in foil.

SUSPENSIONS

Each 5 cc. teaspoonful contains:

Sulfamethazine ..... 167 mg.
Sulfadiazine ..... 167 mg.
Sulfamerazine ..... 167 mg.
} **7½ gr.**

Benzathine penicillin-G
- **100**,000 I.U. — "TRULFACILLIN" 7½-100
- **150**,000 I.U. — "TRULFACILLIN" 7½-150
- **200**,000 I.U. — "TRULFACILLIN" 7½-200
- **300**,000 I.U. — "TRULFACILLIN" 7½-300

DOSE: One to two teaspoonfuls every 4 to 6 hours.

Bottles of 60 cc.

"TRULFACILLIN" PEDIATRIC

SUSPENSIONS

Each 5 cc. teaspoonful contains:

Sulfamethazine ..... 65 mg.
Sulfadiazine ..... 65 mg.
Sulfamerazine ..... 65 mg.
} **3 gr.**

Benzathine penicillin-G
- **100**,000 I.U. — "TRULFACILLIN" PEDIATRIC 3-100
- **200**,000 I.U. — "TRULFACILLIN" PEDIATRIC 3-200

DOSE: Infants and children — one teaspoonful for each 4 pounds of body weight per day in divided doses, e.g., child weighing 8 lb. — ½ teaspoonful every 6 hours; child weighing 16 lb. — 1 teaspoonful every 6 hours.

Bottles of 60 cc.

DROPS

Each 20 drops (1 cc.) contain:

Sulfamethazine ..... 65 mg.
Sulfadiazine ..... 65 mg.
Sulfamerazine ..... 65 mg.
} **3 gr.**

Benzathine penicillin-G ..... **100**,000 I.U. — "TRULFACILLIN" 3-100 DROPS

DOSE: Twenty drops for each 4 pounds of body weight per day in divided doses, e.g., child weighing 8 lb. — 10 drops every 6 hours; child weighing 16 lb. — 20 drops every 6 hours.

Bottles of 10 cc. with precision dropper.

CAUTION

While untoward effects associated with sulfonamide therapy are greatly reduced by the use of Trulfacillin preparations, vigilance should not be relaxed in the search for and recognition of agranulocytosis, fever, joint pains, skin reactions, etc. In rare instances the injection of penicillin, and more rarely still its oral administration, may cause acute anaphylaxis. The reaction appears to occur more frequently in patients with bronchial asthma and other allergies, or in those who have previously demonstrated sensitivity to penicillin.

Charles E. Frosst & Co.
MONTREAL CANADA

WHERE SULFONAMIDES ALONE ARE INDICATED


TRANS WORLD AIRLINES
TWA

ACHROMYCIN*

Tetracycline *Lederle*

in the treatment of

respiratory infections

January and his associates[1] have written on the use of tetracycline (ACHROMYCIN) to treat 118 patients having various infections, most of them respiratory, including acute pharyngitis and tonsillitis, otitis media, sinusitis, acute and chronic bronchitis, asthmatic bronchitis, bronchiectasis, bronchial pneumonia, and lobar pneumonia. Response was judged good or satisfactory in more than 84% of the total cases.

Each month there are more and more reports like this in the literature, documenting the great worth and versatility of ACHROMYCIN. This antibiotic is unsurpassed in range of effectiveness. It provides rapid penetration, prompt control. Side effects, if any, are usually negligible.

No matter what your field or specialty, ACHROMYCIN can be of service to you. For your convenience and the patient's comfort, Lederle offers a *full* line of dosage forms, including

ACHROMYCIN SF

ACHROMYCIN with STRESS FORMULA VITAMINS. Attacks the infection—defends the patient—hastens normal recovery. For severe or prolonged illness. Stress formula as suggested by the National Research Council. Offered in Capsules of 250 mg. and in an Oral Suspension, 125 mg. per 5 cc. teaspoonful.

dry-filled sealed capsules

For more rapid and complete absorption. Offered only by Lederle!

[1]January, H. L. et al: Clinical experience with tetracycline. *Antibiotics Annual* 1954-55, p. 625.

Lederle

LEDERLE LABORATORIES DIVISION
NORTH AMERICAN Cyanamid LIMITED
MONTREAL, QUEBEC

*REG. TRADE MARK IN CANADA

PHOTO DATA: 4X5 VIEW CAMERA, F5.6, 1/25 SEC., EXISTING LIGHTING AT DUSK, ROYAL PAN FILM.

Canad. M. A. J.
June 1, 1956, vol. 74

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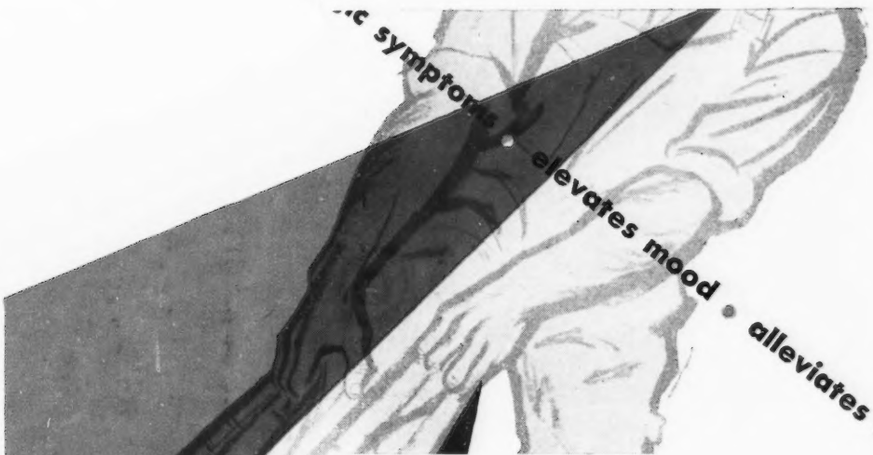
especially formula ıain alert.

• relieves alle c symptoms • elevates mood • alleviates lett gy and depression



one tablet 2 or 3
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h containing 25 mg.
5 mg. Ritalin*;
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erent from the amphe-
and gentler in action,
blood pressure, pulse

eg. trade-marks. 621

CIBA

A new aid for you in the prevention or relief of CONSTIPATION:

Colace

A STOOL SOFTENER, NOT a laxative . . .

* *Helps produce or maintain normal stool hydration*
* *Avoids unnatural stimulation of bowel activity*

Advantages

COLACE

— is a *stool softener*, and produces a soft stool by causing, maintaining or increasing hydration of the stool.

— is **not** a cathartic, laxative, or purgative.

— does **not** produce intestinal griping; does **not** produce its effect by intestinal irritation; does **not** produce loose watery stools; does **not** cause "leakage" from the anus; does **not** decrease in effectiveness even when used for indefinite periods of time.

— is nontoxic even when taken in large amounts. (1) (3)

Availability

— LIQUID, 1% solution (10 mg. per cc.) in 30 cc. bottle with plastic dropper, calibrated at 1 cc.

— CAPSULES, 50 mg. soft gelatin capsules, bottles of 60.

For additional details, ask your MEAD representative or drop a postcard to 600 University Avenue, Toronto.

CLINICAL REFERENCES:

(1) *Wilson, J. L., and Dickinson, G. C.: Use of Dioctyl Sodium Sulfosuccinate (Aerosol O.T.) For Severe Constipation, J.A.M.A. 158: 261-3 May 28, 1955.*

(2) *Towsley, H.A.: The Constipated Infant, Michigan State Med. Soc., J. 54: 1064-1066, 1138, Sept. 1955.*

(3) *Benaglia, A.E.; Robinson, E.J.; Utley, E. and Cleverdon, M.A.: The Chronic Toxicity of Aerosol—OT, J. Indust. Hyg. & Toxicol. 25: 175, May, 1943.*

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